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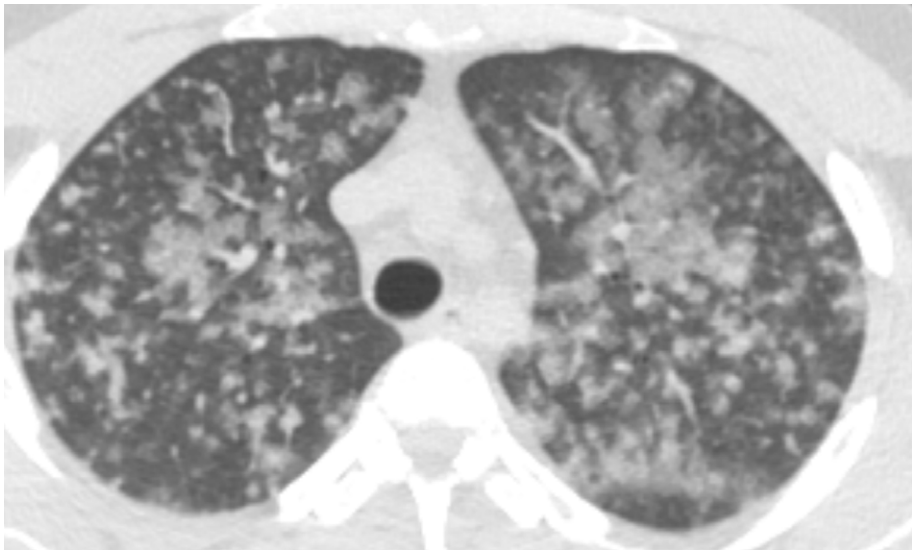

A young farmer with dyspnoea; what is your diagnosis?

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EDITORIAL

Distrusting confidence

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I remember my first out-of-hours service vividly. The fear and agony were immense. I had been a resident for just a few weeks and there I was, alone, responsible for over 60 beds and a crowded downtown Amsterdam Emergency Room. I was convinced that the first person needing resuscitation was gonna be me. But no one died. The ER personnel, particularly some of the older nurses, knew exactly who they were dealing with, offered guidance and support, and pretty much pulled me and my patients through the night.

Needless to say I didn't feel ready for doing shifts at the time, but nor did I for several years afterwards. And believe it or not, I still sometimes feel not-ready for doing what I am supposed to do, and what others might think I am well-qualified for. My latest weekend supervision, for example, I started feeling insecure and tense. No one noticed, I guess, and once I was doing rounds on the ER and wards, the feeling gradually subsided.

Elsewhere in this issue, Baten et al. report that many residents feel insufficiently prepared for their first out-of-hours service.[1] Among other factors, having at least a few months of experience and some form of targeted training and assessment offered some protection against 'feeling unready'. The authors find this disconcerting, and argue that the results actually reflect insufficient preparation of residents starting out-of-hours service.

However much I sympathise with junior residents starting out-of-hours service, I think *feeling* ready is a very poor substitute for *being* ready. Having said that, I unreservedly acknowledge that, particularly in the old days, many residents start(ed) doing shifts almost totally unprepared, harming themselves and patients alike. Has that caused casualties? Certainly so. Residents entering shifts which include responsibility for critically ill patients should have at least several months of clinical experience. Targeted training is mandatory in most hospitals and specialties and apparently boosts self-confidence, although I am uncertain if it really improves care and patient safety. Before a resident starts doing shifts, the supervisors should explicitly agree that the necessary medical and communicative skills are up to standards.

If all the above conditions have been met, residents will start their first shift sufficiently prepared, but feeling either very secure, completely insecure or, most often, somewhere in between. 'Who would I like to look after my sick family', is a question that reportedly correlates well with residents' quality of care. For me, the answer is easy: get me an insecure one. I just don't trust self-confidence.

We should make sure that residents starting out-of-hours service are adequately prepared. If they *feel* unprepared nonetheless, we need to address that, but the message must be that it is okay to feel insecure, that we trust and support them, and that help is never far away. Along the way of medical training and professional careers, we must remember that feeling insecure is a virtue, protecting us from over-confidence and cutting corners.

REFERENCE

1. Baten A, Bleeker-Rovers CP, van den Heijkant F, de Graaf J, Fluit CRMG. Residents' readiness for out-of-hours service: a Dutch national survey. Neth J Med. 2018;76:78-83.

REVIEW

Nonsteroidal anti-inflammatory drug hypersensitivity: not always an allergy!

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a major cause of hypersensitivity reactions. Several distinct clinical syndromes are described regarding NSAID hypersensitivity. Such a reaction is generally caused by a non-immunological mechanism. In susceptible patients, COX-1 inhibition leads to an imbalance in lipid mediators such as leukotrienes and prostaglandins. It is essential to distinguish multiple nonspecific NSAID hypersensitivity from single NSAID hypersensitivity, since the management of these respective syndromes is essentially different. This review provides an overview on all the aspects of NSAID hypersensitivity reactions, from pathophysiology to clinical symptoms, leading practical recommendations.

KEYWORDS

Acetylsalicylic acid, asthma, drug allergy, hypersensitivity, nonsteroidal anti-inflammatory drugs

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most used drugs worldwide. It is therefore not surprising that they are a major cause of hypersensitivity reactions, accounting for up to 48.7% of drug-related 'allergic' reactions.[1-3] Various mechanisms are distinguished through which NSAIDs can cause hypersensitivity reactions in humans, all leading to quite similar symptoms making it difficult to determine the cause in a specific patient. Adding to the confusion of clinicians is the different terminology and many abbreviations that are used in the medical literature. This review provides an overview of the pathophysiology and clinical aspects of NSAID hypersensitivity and ends with practical recommendations.

CASE 1

A 35-year-old male presents to his general practitioner because of alleged reactions to various NSAIDs. He recalls that he had his first reaction about ten years ago consisting of swelling and redness of the eyes shortly after ingestion of ibuprofen. One year ago, swelling of the lips occurred one hour after ingestion of naproxen. Recently, similar symptoms developed three hours after the ingestion of 1000 mg of acetaminophen. His medical history reveals childhood asthma, and mild allergic rhinoconjunctivitis in the spring. He does not take any daily medications. He asks which analgesic he can safely use after an upcoming dentist procedure.

What is the correct diagnosis and what advice should the patient receive?

CASE 2

A 56-year-old male is referred to the Allergy outpatient clinic because of a recent reaction to diclofenac. The patient endured an accident when cycling and had several bruised ribs for which diclofenac 50 mg, three times daily, was prescribed. On the third day, he developed rapidly progressive urticaria, abdominal cramps, and started perspiring heavily, 30 minutes after ingestion of diclofenac. He did not notice any respiratory symptoms. At the Emergency Department, hypotension was found. He has used ibuprofen, diclofenac and acetaminophen in the past without any reactions.

What is the correct diagnosis and what test could aid in this diagnosis?

CASE 3

A 30-year-old woman presents with dyspnoea after taking ibuprofen for a sprained ankle. One hour after the first dose, nasal congestion and dyspnoea occurred. When she presented at the Emergency Department, severe wheezing was noted. The patient did not have a rash or angioedema. She was treated with salbutamol inhalation, intravenous corticosteroids and xylometazoline nose spray. The medical history of the patient revealed constitutional eczema and atopic asthma for which she used high doses of inhaled corticosteroids with a long-acting beta agonist.
What is the correct diagnosis and which analgesics are safe for this patient?

PATHOPHYSIOLOGY OF NSAID HYPERSENSITIVITY

NSAIDs are a large group of drugs that block the enzyme cyclooxygenase (COX), thereby inhibiting the production of prostaglandins from arachidonic acid.[4] *Figure 1* provides an overview of the most used NSAIDs. Arachidonic acid is metabolised by two pathways: the COX pathway, which induces synthesis of prostaglandins, and the lipoxygenase pathway, which induces synthesis of cysteinyl-leukotrienes and thromboxane. There are at least two isoforms of COX. COX-1 is constitutively expressed by specific cells such as thrombocytes and endothelial cells. COX-2 is inducible by pro-inflammatory mediators in a wide variety of cells.[4] In susceptible patients, COX-1 blockade leads to a relative increase in cysteine-leukotriene synthesis causing inflammation of the respiratory tract.[5,6] This is due to a constitutively disrupted balance between pro- and anti-inflammatory prostaglandins and leukotrienes in patients with multiple NSAID hypersensitivity (*figure 2*). Here, pro-inflammatory cysteinyl-leukotrienes are continually upregulated and the anti-inflammatory prostaglandin E_2 is downregulated.[7-9] The latter appears to be a consequence of the downregulation of COX-2.[6,10] When COX-1 is then blocked by an NSAID, the prostaglandin production is further decreased. This amplifies the pre-existent imbalance in favour of the cysteinyl-leukotrienes, which can induce bronchospasm, vascular leakage, eosinophilic inflammation and mast cell activation.[9,11,12] Although cysteinyl-leukotrienes appear to play a main role in the mechanism for NSAID-exacerbated respiratory disease (NERD) and NSAID-exacerbated cutaneous disease (NECD), there is evidence for additional

Figure 1. *Visual summary of the COX-1 and/or COX-2 inhibiting properties of the most used NSAIDs in the Netherlands. Ketorolac and indomethacin are strong COX-1 inhibitors.[49,50] Rofecoxib and etoricoxib are the most selective COX-2 inhibitors*

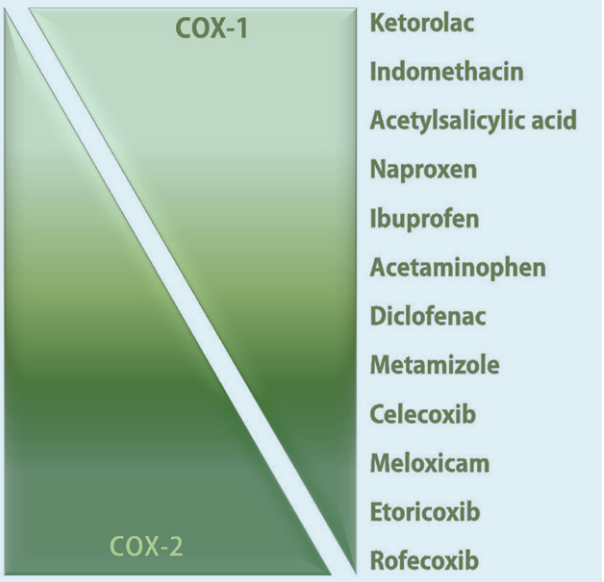
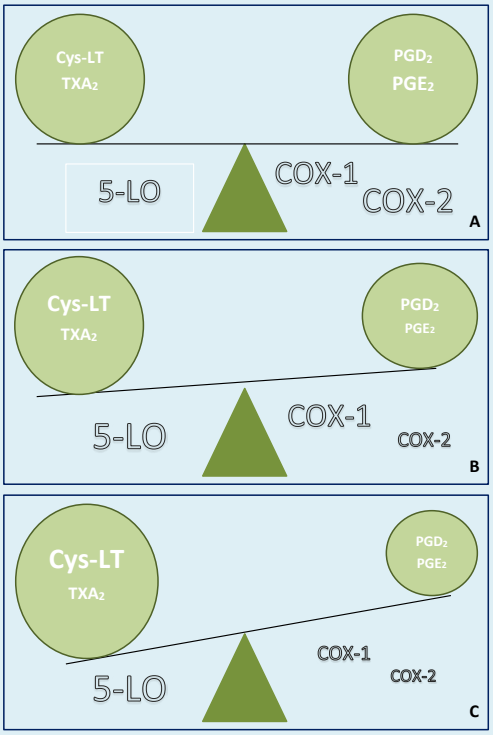


Figure 2. *Schematic figure showing the pathophysiology of multiple NSAID hypersensitivity syndrome*



The enzymes cyclooxygenase (COX) and 5-lipoxygenase (5-LO) regulate the production of prostaglandins and thromboxane, and leukotrienes, respectively, from arachidonic acid. Under physiological circumstances, pro- and anti-inflammatory eicosanoids are balanced to maintain homeostasis (panel A). In NERD, the levels of pro-inflammatory cysteinyl-leukotrienes (cys-LT) are elevated. Moreover, the levels of the anti-inflammatory prostaglandin E_2 (PGE_2) are decreased due to downregulation of COX-2 (panel B). The use of NSAIDs leads to further imbalance by blocking COX-1, and often also COX-2 (panel C), thereby causing clinical symptoms due to a relative overload of pro-inflammatory cysteinyl-leukotrienes.[5,6,8]

roles of both TH_1 and TH_2 cells, granulocytes, and thrombocytes.[11,13,14]

DIFFERENT FORMS OF NSAID HYPERSENSITIVITY

There are four clinical phenotypes of immediate-type NSAID hypersensitivity: NERD, NECD, NSAID induced urticaria/angioedema (NIUA), or single NSAID induced urticaria/angioedema/anaphylaxis (SNIUAA). The last mentioned is a specific, probably IgE-mediated, allergy. The other phenotypes do not have an immunological pathophysiology, but are caused by inhibiting of COX-1 resulting in an imbalance in eicosanoid mediators, as outlined further. The terms *pseudo-allergy* and *intolerance* were commonly used in the past to indicate this type of reaction but are outdated.[15] Next to these immediate-type hypersensitivity syndromes, a delayed-type hypersensitivity syndrome is termed 'single NSAID-induced delayed type reaction' (SNIDR).

NON-IMMUNOLOGICALLY MEDIATED (CROSS-REACTIVE) NSAID INDUCED HYPERSENSITIVITY REACTIONS

NSAID-exacerbated respiratory disease (NERD)

This phenotype is also known as aspirin-exacerbated respiratory disease or the 'acetylsalicylic acid (ASA) triad'.[15] Around 7-14% of adult asthma patients have NERD.[16,17] Contrary to allergic asthma, NERD commonly starts in early adulthood.[18] It is characterised by refractory polyposis nasi, sinusitis, modest to severe asthma, and hypersensitivity reactions to various types of NSAID with COX-1 inhibiting properties. The asthma is often severe and corticosteroid-dependent. However, not all patients have the full triad, as rhinosinusitis typically precedes asthma by 1-3 years. Consequently, not all patients have clinically overt asthma: they may experience their first 'asthma exacerbation' only after NSAID ingestion.[18] Many patients have anosmia and often need sinus surgery.[14] Ingestion of an NSAID (mainly, but not exclusively, those with strong COX-1 inhibition) will lead to an exacerbation of asthma and/or rhinitis and sometimes also angioedema. The reaction can be delayed for several hours. The mean provoking dose was around 80 mg in different studies; however, reactions are described at doses as low as 10 mg.[16,19]

NSAID-exacerbated cutaneous disease (NECD)

NECD is actually the cutaneous variant of NERD. Patients with NECD suffer from chronic spontaneous urticaria (CSU) and/or angioedema and experience worsening of these symptoms after the ingestion of an NSAID.[20] Although most reactions include urticaria, isolated angioedema is a possible manifestation of NECD.[21] The incidence of NECD is estimated to be 12-30% in CSU patients.[22] NECD patients did not react to selective COX-2 inhibitors in several studies.[23,24]

Since CSU is often a self-limiting disease within months to years, NECD can potentially recover with the resolution of CSU. However, NECD patients seem to have a distinct phenotype compared with NSAID-tolerant CSU patients: the latter have a shorter duration of CSU and less often have angioedema when compared with NECD patients.[25] To our knowledge, there are no comprehensive data on the resolution of NECD.

NSAID-induced urticaria/angioedema (NIUA)

Patients with NIUA do not have spontaneous urticaria and/or angioedema, but only develop them after the ingestion of an NSAID. As with NERD and NECD, NIUA is a multiple NSAID hypersensitivity syndrome and there is cross-reactivity between chemically nonrelated NSAIDs.[22] Since patients often start to avoid NSAIDs after their first reaction, this cross-reactivity might not always be clear. Patients can report isolated urticaria, angioedema or a combination of both. Approximately 60% of all patients with NIUA have concomitant atopic disease, although a hypothesis for a pathophysiological mechanism for this association is lacking.[22,26] The pathophysiological basis for NIUA appears similar to that of NERD and NECD, as several polymorphisms were detected in genes related to arachidonic acid metabolism.[27,28] Spanish studies reveal that 62% of NIUA patients spontaneously develop tolerance to NSAIDs after five years. Risk factors for persistent NSAID hypersensitivity are atopy and isolated angioedema.[29,30] Conversely, 33% of patients with NIUA developed chronic spontaneous urticaria during follow-up.[31] These patients thus actually had NECD with delayed presentation of the spontaneous urticaria.

IMMUNOLOGICALLY MEDIATED SPECIFIC NSAID HYPERSENSITIVITY REACTIONS

Single NSAID induced urticaria/angioedema or anaphylaxis (SNIUAA)

SNIUAA is biologically and phenotypically distinct from the other NSAID hypersensitivity syndromes. Patients only react to one NSAID or multiple NSAIDs with similar chemical structures. It usually consists of a rapid, systemic anaphylactic reaction, resembling type-I hypersensitivity.[3,32] Reactions are generally more severe than in the previous syndromes. SNIUAA can also present with isolated urticaria and/or angioedema, although

isolated angioedema is unlikely. The fact that patients with SNIUAA can tolerate other NSAIDs than the culprit drug suggests a sensitisation for a certain epitope in the NSAID in question. Until now, sensitisation tests such as specific IgE measurement and skin testing were often negative.[3,33] Possibly, there is only a small time window in which specific IgE is detectable, or the reaction might not be IgE mediated at all.[34]

Single NSAID induced delayed reactions (SNIDR)

SNIDR is a highly heterogeneous group of clinical entities usually occurring within 24-48 hours after the ingestion of an NSAID. The entities range from mild reactions such as a maculopapular rash, to severe allergic syndromes such as acute generalised exanthematous pustulosis or toxic epidermal necrolysis.[35] The putative mechanism is T-cell mediated. Due the fact that these reactions can be life-threatening, randomised studies are lacking and the possibility of cross-reactivity has not been elucidated. Because the scope of this review is immediate-type NSAID hypersensitivity reactions, SNIDR will not be discussed further.

DIAGNOSTIC STRATEGIES

All patients with a reaction to an NSAID should be advised to avoid all NSAIDs until more certainty is obtained about cross-reactivity. As outlined previously, SNIUAA typically presents with acute, systemic reactions to the culprit drug, and tolerance to other NSAIDs. However, the clinical symptoms of the above-described hypersensitivity syndromes can overlap, since SNIUAA can also present with isolated urticaria, and patient histories are not always reliable.[36] Furthermore, most patients avoid NSAIDs after their first reaction, and information on clinical cross-reactivity is lacking. Comorbidities can aid in the diagnosis: patients with a history of chronic spontaneous urticaria or a combination of asthma, rhinitis, and nasal polyps are likely to be multiple reactors (*table 1*).

Common allergologic diagnostic procedures are not suitable for NSAID hypersensitivity. The European Academy of Allergy and Clinical Immunology (EAACI) position paper does not recommend skin tests as part of the diagnostic work up.[37] Specific IgE and basophil activation tests are not reliable in this context.[3,15,38] There is also no association between NSAID hypersensitivity and serum tryptase levels.[39] Since multiple NSAID reactors have raised levels of prostaglandin D_2 and leukotriene E_4, measurement of these levels might identify persons at risk for NSAID hypersensitivity.[7,40,41] However, these cannot be used for a final diagnosis.

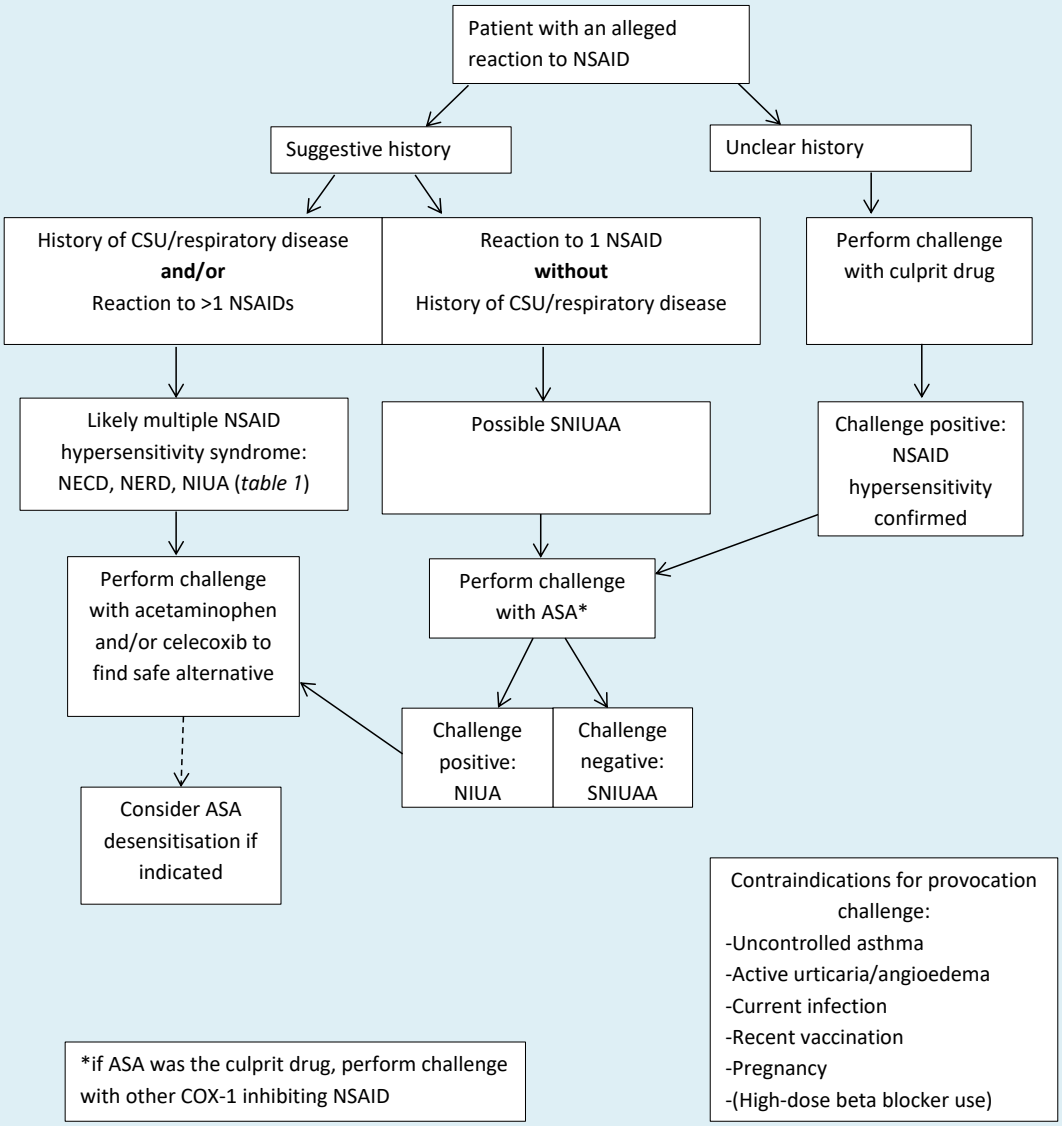
A provocation challenge remains the gold standard.[22] The goal of such a drug challenge can be twofold; it can either establish the diagnosis or identify a safe alternative NSAID. Since ASA is among the strongest COX-1 inhibitors (*figure 1*), this is often used to test for general NSAID hypersensitivity, depending on the patient history and anticipated risk of the provocation challenge itself.[42] See *figure 3* for a decision model. Contraindications for a provocation challenge are: severe asthma (FEV1 < 70% of predicted, use of short-acting beta-agonist ≥ 3 times a week, nightly dyspnoea), active spontaneous urticaria/angioedema in the last two weeks, pregnancy, active infection, and a recent vaccination (≤ 1 week). Relative contraindications are the use of beta-blockers or ACE-inhibitors.[22,43] In order to avoid false-negative results, histamine and leukotriene antagonists need to

Table 1. *Summary of different NSAID hypersensitivity syndromes*

Timing of reaction	≤ 24 hours			≤ 2 hours
Reaction to multiple NSAIDs?	Yes		Yes	No
Type of reaction	Urticaria and/or angioedema		Bronchospasm, nasal congestion, rhinorrhoea	Anaphylaxis*
Underlying disease	None†	Chronic spontaneous urticaria and/or angioedema	Asthma with polyposis nasi, and/or chronic recurring sinusitis	None
Diagnosis	**NIUA**	**NECD**	**NERD**	**SNIUAA**
Risk of reaction to COX-2 inhibitor[23,24]	6%-25%‡	17.4%	0-8.7%	0%
Risk of reaction to acetaminophen[24]	12.5%	43.9%	33.3%	0%

NIUA = NSAID-induced urticaria/angioedema ; NECD = NSAID exacerbated cutaneous disease ; NERD = NSAID exacerbated respiratory disease ; SNIUAA = single NSAID induced urticaria/angioedema or anaphylaxis.
*Only urticaria also possible; †Approximately 60% of patients with NIUA have atopic disease; ‡Risk 6% if acetaminophen tolerant, and 25% for patients who also have acetaminophen hypersensitivity.

Figure 3. *Flowchart of the decision process regarding the management of a patient who has one or more reported immediate-type reactions to NSAIDs which has raised the suspicion of NSAID hypersensitivity*



be discontinued at least three days before the challenge.[44] Inhalation medication for asthma should be continued for safety reasons. The use of a standardised scoring system and a double-blind, placebo-controlled format can increase the reliability of a drug challenge.[45]

If a patient has a history of multiple NSAID reactions and/or spontaneous urticaria, angioedema or chronic respiratory disease (asthma, rhinitis etc.), the likelihood of multiple NSAID hypersensitivity is very high. A challenge with ASA can in such cases cause cumbersome symptoms or even life-threatening asthma exacerbations. Therefore, it is preferred to directly perform a challenge with an alternative, for instance a specific COX-2 inhibitor, in these patients. When SNIUAA is assumed, it can be unnecessarily hazardous to challenge the patient with the culprit drug. It is then preferred to perform a challenge with ASA to exclude a multiple NSAID hypersensitivity syndrome. If ASA is tolerated well, the patient is advised to only avoid the culprit NSAID, and other classes will be safe. The patients that present with isolated urticaria after NSAID ingestion without any relevant history are the most difficult to categorise. With the aforementioned strategy, they would first undergo ASA challenge to distinguish between NIUA or SNIUAA. Often, the history is not clear at all, and the first goal is to establish any type of causality between the NSAID ingestion and the reaction. Depending on the severity of the previous reaction, a challenge with the culprit drug can then be performed first. If that

challenge is negative, any type of NSAID hypersensitivity can be excluded. If the challenge to the culprit drug is positive, the Allergist can decide to challenge with ASA to further distinguish between single or multiple NSAID hypersensitivity. Of note, drug challenges always pose a certain risk, depending on the phenotype of the patient, as outlined previously. Therefore, these challenges should be performed by experienced Allergists with the appropriate resources and access to emergency medical care.

AFTER THE DIAGNOSIS: ALTERNATIVE ANALGESICS AND DESENSITISATION

Depending on the diagnosis and outcome of the ASA challenge, the patient can be advised to avoid only the culprit or all NSAIDs. Then, there might be a need to investigate the safety of alternative analgesics. The risk of hypersensitivity reactions to acetaminophen varies between the different subtypes of NSAID hypersensitivity. Numbers between 9.6% and 43.9% have been reported.[24,46] It is advised to perform a challenge that ends with a sufficiently high dose of acetaminophen (1000 mg) in all patients with multiple NSAID hypersensitivity. Selective COX-2 inhibitors are often a safe alternative, especially in patients who can tolerate acetaminophen. In the latter, only 6% of patients with NIUA reacted to a selective COX-2 inhibitor, and in NERD, the risk was actually zero.[23,47] It must be noted that the patients in these studies had mild-to-moderate asthma, and the risk of reaction to a COX-2 inhibitor in patients with severe asthma might be higher. Since there are no similar studies among patients with NERD and severe asthma, it is advisable to treat the asthma appropriately before performing any drug challenge. Patients with NECD have the highest risk of cross-reactivity with both acetaminophen and selective COX-2 inhibitors (*table 2*). Thus, an additional challenge with a specific COX-2 inhibitor should be the next step in the evaluation of patients with multiple NSAID hypersensitivity, especially when they have also reacted to acetaminophen. Re-evaluation after five to six years can be considered in patients with NECD or NIUA, because a substantial number develop tolerance to all NSAIDs.[29,30] Patients with cardiovascular disease are often recommended to use a daily low dose of up to 100 mg ASA, which can cause a problem for multiple NSAID reactors. Fortunately, low doses are often tolerated. If patients do react to these low doses, ASA desensitisation can be attempted. Desensitisation is a procedure aimed at inducing a pharmacological or immunological tolerance to the drug. There is no international standard for this procedure and many different desensitisation schedules are described in the literature. Of course, it is essential that the patient's asthma is well controlled. *Table 2* provides two possible schedules for desensitisation.[48] Daily use of ASA after the desensitisation is necessary to maintain tolerance.

CONCLUSIONS

There are several different NSAID hypersensitivity syndromes. The distinction between multiple and single NSAID reactivity is pivotal and can largely be made based on the patient's history. Provocation challenges are the gold standard to confirm NSAID hypersensitivity, or to find safe alternatives. ASA desensitisation is a safe and effective method for patients who have a strict indication.

ANSWERS

Case 1

The reactions to different NSAIDs and the time lag between ingestion and reaction are suggestive of a multiple NSAID hypersensitivity syndrome. Furthermore, the absence of current asthma, sinusitis, rhinitis, nasal polyps or spontaneous urticaria/angioedema argues

Table 2. *Examples of acetylsalicylic acid desensitisation schedules*

Time (hour)	Dose (mg)	Cumulative dose (mg)
Fast schedule		
08:00	30	30
10:00	60	90
12:00	100	190
14:00	325	515
16:00	650	1165
18:00	End of desensitisation	
Slow schedule		
Day 1:		
8:00	30	30
11:00	60	90
14:00	100	190
17:00	End of day 1	
Day 2		
8:00	150	150
11:00	325	475
14:00	650	1125
17:00	End of desensitisation	

for a diagnosis of NIUA. Up to 25% of patients with NIUA also have hypersensitivity reactions to high-dose acetaminophen (i.e., ≥ 1000 mg) thus it is not surprising that the patient reported reactions to acetaminophen too. A selective COX-2 inhibitor, such as celecoxib, is tolerated in most patients with NIUA. To find out, it was advised to perform an open provocation challenge with celecoxib.

Case 2

This patient had generalised urticaria with hypotension, fulfilling the definition of severe anaphylaxis, rapidly after ingestion of diclofenac. This clinical pattern, combined with the fact that he did not have respiratory disease or CSU, is suggestive of a specific diclofenac allergy (SNIUAA). Because this case is clear-cut, a challenge with diclofenac is not needed to establish the diagnosis. Even in case of a doubtful history, a challenge test with diclofenac should be avoided because of a possible severe reaction during challenge. In this patient a challenge test with ASA is indicated to find out if alternative NSAIDs can be tolerated.

Case 3

It is highly likely that this patient has NERD, because of the combination of respiratory distress with nasal congestion and the medical history of moderately severe asthma. She should be advised to avoid all classic NSAIDs. A challenge with COX-2 would be useful to find out whether this is a safe alternative for her. The risk of hypersensitivity reactions to acetaminophen is negligible for patients with NERD.

DISCLOSURES

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REFERENCES

1. Aun MV, Blanca M, Garro LS, et al. Nonsteroidal anti-inflammatory drugs are major causes of drug-induced anaphylaxis. J Allergy Clin Immunol Pract. 2014;2:414-20.
2. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol. 2005;5:309-16.
3. Rebelo Gomes E, Geraldes L, Gaspar A, et al. Hypersensitivity Reactions to Nonsteroidal Anti-Inflammatory Drugs among Adults: Clinical Features and Risk Factors for Diagnosis Confirmation. Int Arch Allergy Immunol. 2016;171:269-75.
4. Rao P, Knaus EE. Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond. J Pharm Pharm Sci. 2008;11:81s-110s.
5. Parker AR, Ayars AG, Altman MC, Henderson WR, Jr. Lipid Mediators in Aspirin-Exacerbated Respiratory Disease. Immunol Allergy Clin North Am. 2016;36:749-63.
6. Steinke JW, Wilson JM. Aspirin-exacerbated respiratory disease: pathophysiological insights and clinical advances. J Asthma Allergy. 2016;9:37-43.
7. Hagan JB, Laidlaw TM, Divekar R, et al. Urinary Leukotriene E4 to Determine Aspirin Intolerance in Asthma: A Systematic Review and Meta-Analysis. J Allergy Clin Immunol Pract. 2017;5:990-7.
8. Laidlaw TM, Boyce JA. Pathogenesis of aspirin-exacerbated respiratory disease and reactions. Immunol Allergy Clin North Am. 2013;33:195-210.
9. Cahill KN, Laidlaw TM. Pathogenesis of Aspirin-Induced Reactions in Aspirin-Exacerbated Respiratory Disease. Immunol Allergy Clin North Am. 2016;36:681-91.
10. Oussalah A, Mayorga C, Blanca M, et al. Genetic variants associated with drugs-induced immediate hypersensitivity reactions: a PRISMA-compliant systematic review. Allergy. 2016;71:443-62.
11. Laidlaw TM, Boyce JA. Aspirin-Exacerbated Respiratory Disease--New Prime Suspects. N Engl J Med. 2016;374:484-8.
12. Steinke JW, Negri J, Liu L, Payne SC, Borish L. Aspirin activation of eosinophils and mast cells: implications in the pathogenesis of aspirin-exacerbated respiratory disease. J Immunol. 2014;193:41-7.
13. Laidlaw TM, Boyce JA. Platelets in patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2015;135:1407-14; quiz 15.
14. Woessner KM. Update on Aspirin-Exacerbated Respiratory Disease. Curr Allergy Asthma Rep. 2017;17:2.
15. Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. Allergy. 2013;68:1219-32.
16. Morales DR, Guthrie B, Lipworth BJ, Jackson C, Donnan PT, Santiago VH. NSAID-exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. Allergy. 2015;70:828-35.
17. Rajan JP, Wineinger NE, Stevenson DD, White AA. Prevalence of aspirin-exacerbated respiratory disease among asthmatic patients: A meta-analysis of the literature. J Allergy Clin Immunol. 2015;135:676-81.e1.
18. Kennedy JL, Stoner AN, Borish L. Aspirin-exacerbated respiratory disease: Prevalence, diagnosis, treatment, and considerations for the future. Am J Rhinol Allergy. 2016;30:407-13.
19. Schuler CFt, Baldwin JL, Baptist AP. Frequency and severity of reactions to a 325-mg aspirin dose during desensitization. Ann Allergy Asthma Immunol. 2017;118:333-8.e1.
20. Sanchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Aspirin-exacerbated cutaneous disease. Immunol Allergy Clin North Am. 2013;33:251-62.
21. Leeyaphan C, Kulthanan K, Jongjarearnprasert K, Dhana N. Drug-induced angioedema without urticaria: prevalence and clinical features. J Eur Acad Dermatol Venereol. 2010;24:685-91.
22. Kowalski ML, Woessner K, Sanak M. Approaches to the diagnosis and management of patients with a history of nonsteroidal anti-inflammatory drug-related urticaria and angioedema. J Allergy Clin Immunol. 2015;136:245-51.
23. Dona I, Blanca-Lopez N, Jagemann LR, et al. Response to a selective COX-2 inhibitor in patients with urticaria/angioedema induced by nonsteroidal anti-inflammatory drugs. Allergy. 2011;66:1428-33.
24. Kim YJ, Lim KH, Kim MY, et al. Cross-reactivity to Acetaminophen and Celecoxib According to the Type of Nonsteroidal Anti-inflammatory Drug Hypersensitivity. Allergy Asthma Immunol Res. 2014;6:156-62.
25. Sanchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A, Gonzalez-Aveledo L. Aspirin-exacerbated cutaneous disease (AECD) is a distinct subphenotype of chronic spontaneous urticaria. J Eur Acad Dermatol Venereol. 2015;29:698-701.
26. Sanchez-Borges M, Acevedo N, Caraballo L, Capriles-Hulett A, Caballero-Fonseca F. Increased total and mite-specific immunoglobulin E in patients with aspirin-induced urticaria and angioedema. J Investig Allergol Clin Immunol. 2010;20:139-45.
27. Cornejo-Garcia JA, Jagemann LR, Blanca-Lopez N, et al. Genetic variants of the arachidonic acid pathway in non-steroidal anti-inflammatory drug-induced acute urticaria. Clin Exp Allergy. 2012;42:1772-81.
28. Cornejo-Garcia JA, Liou LB, Blanca-Lopez N, et al. Genome-wide association study in NSAID-induced acute urticaria/angioedema

in Spanish and Han Chinese populations. Pharmacogenomics. 2013;14:1857-69.

29. Dona I, Barrionuevo E, Salas M, et al. Natural evolution in patients with nonsteroidal anti-inflammatory drug-induced urticaria/angioedema. Allergy. 2017.
30. Dona I, Blanca-Lopez N, Torres MJ, Gomez F, Fernandez J, Zambonino MA, et al. NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study. Allergy. 2014;69:438-44.
31. Asero R. Intolerance to nonsteroidal anti-inflammatory drugs might precede by years the onset of chronic urticaria. J Allergy Clin Immunol. 2003;111:1095-8.
32. Woessner KM, Castells M. NSAID single-drug-induced reactions. Immunol Allergy Clin North Am. 2013;33:237-49.
33. Harrer A, Lang R, Grims R, et al. Diclofenac hypersensitivity: antibody responses to the parent drug and relevant metabolites. PLoS One. 2010;5:e13707.
34. Blanca M, Perez E, Garcia JJ, et al. Angioedema and IgE antibodies to aspirin: a case report. Ann Allergy. 1989;62:295-8.
35. Demir S, Olgac M, Unal D, Gelincik A, Colakoglu B, Buyukozturk S. Evaluation of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs according to the latest classification. Allergy. 2015;70:1461-7.
36. Viola M, Rumi G, Valluzzi RL, Gaeta F, Caruso C, Romano A. Assessing potential determinants of positive provocation tests in subjects with NSAID hypersensitivity. Clin Exp Allergy. 2011;41:96-103.
37. Kowalski ML, Makowska JS, Blanca M, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) - classification, diagnosis and management: review of the EAACI/ENDA(#) and GA2LEN/HANNA*. Allergy. 2011;66:818-29.
38. Mitsui C, Kajiwara K, Ono E, et al. Analysis of basophil activation in patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2017;4:1162-4.
39. Seitz CS, Brockow K, Hain J, Trautmann A. Non-steroidal anti-inflammatory drug hypersensitivity: association with elevated basal serum tryptase? Allergy Asthma Clin Immunol. 2014;10:19.
40. Cahill KN, Bensko JC, Boyce JA, Laidlaw TM. Prostaglandin D(2): a dominant mediator of aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2015;135:245-52.
41. Daffern PJ, Muilenburg D, Hugli TE, Stevenson DD. Association of urinary leukotriene E4 excretion during aspirin challenges with severity of respiratory responses. J Allergy Clin Immunol. 1999;104(3 Pt 1):559-64.
42. Perez-Alzate D, Cornejo-Garcia JA, Perez-Sanchez N, et al. Immediate Reactions to More Than 1 NSAID Must Not Be Considered Cross-Hypersensitivity Unless Tolerance to ASA Is Verified. J Investig Allergol Clin Immunol. 2017;27:32-9.
43. Agache I, Bilo M, Braunstahl GJ, et al. In vivo diagnosis of allergic diseases--allergen provocation tests. Allergy. 2015;70:355-65.
44. White AA, Bosso JV, Stevenson DD. The clinical dilemma of 'silent desensitization' in aspirin-exacerbated respiratory disease. Allergy Asthma Proc. 2013;34:378-82.
45. Cook KA, Modena BD, Wineinger NE, Woessner KM, Simon RA, White AA. Use of a composite symptom score during challenge in patients with suspected aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2017;118:597-602.
46. Nettis E, Marcandrea M, Ferrannini A, Tursi A. Tolerability of nimesulide and paracetamol in patients with NSAID-induced urticaria/angioedema. Immunopharmacol Immunotoxicol. 2001;23:343-54.
47. Morales DR, Lipworth BJ, Guthrie B, Jackson C, Donnan PT, Santiago VH. Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: Meta-analysis of controlled clinical trials. J Allergy Clin Immunol. 2014;134:40-5.
48. Cortellini G, Romano A, Santucci A, et al. Clinical approach on challenge and desensitization procedures with aspirin in patients with ischemic heart disease and nonsteroidal anti-inflammatory drug hypersensitivity. Allergy. 2017;72:498-506.
49. Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. Am J Med. 1998;104:413-21.
50. Vane SJ. Aspirin and other anti-inflammatory drugs. Thorax. 2000;55 Suppl 2:S3-9.

REVIEW

Clinical value of serum lactate measurement in diagnosing acute mesenteric ischaemia

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ABSTRACT

Acute mesenteric ischaemia (AMI) is a life-threatening disease with a mortality rate around 60%. This high mortality rate is largely caused by diagnostic delay, which means there is a pressing need for a reliable biomarker. In clinical practice, serum lactate measurement is often used for the diagnosis of AMI. To assess the diagnostic value of serum lactate, we performed a literature search.
Lactate has two different isomers. The well-known L-lactate, produced by anaerobic glycolysis, and the more unknown D-lactate which is only produced by intestinal bacteria. In this review, we present and evaluate the current literature on the diagnostic value of the measurement of both lactate isomers. Furthermore, we suggest another biomarker which might have the potential to serve as a useful diagnostic test in the future.

KEYWORDS

Intestinal ischaemia, L-lactate, D-lactate

INTRODUCTION

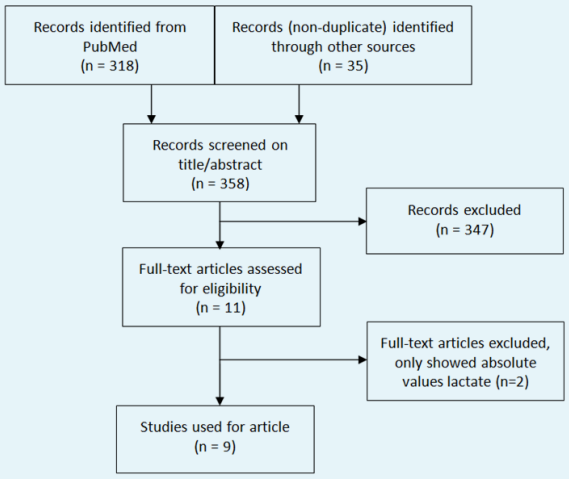
One of the possible causes of severe abdominal pain is acute mesenteric ischaemia (AMI), a life-threatening disease with a high mortality rate. The in-hospital mortality is around 60%.[1] Based on aetiology there are four types of AMI. Most frequently, accountable for approximately 40-50% of the cases, AMI is caused by an arterial embolism from the heart or proximal aorta. In 25-30% of the cases AMI is caused by arterial thrombosis in an atherosclerotic splanchnic artery. Non-occlusive mesenteric ischaemia is responsible for approximately 20% of the mesenteric ischaemic events which may for example be due to hypovolaemia, as systemic vasoconstriction induces splanchnic hypoperfusion. Finally, the least common type is mesenteric venous thrombosis which occurs in around 10% of the patients.[2]
The high mortality rate is largely caused by diagnostic delay in this fast-progressing disease,[3] although significant comorbidity in patients with AMI also plays a role. Clinical symptoms such as pain often do not correlate with other clinical signs, such as signs of peritonitis.[4,5] Therefore the need for a reliable and accurate diagnostic test is high. Prior to imaging, many clinics measure the serum lactate concentration as part of the diagnostic work-up for the diagnosis of intestinal ischaemia.
There are two different isomers of lactate: D-lactate and L-lactate. L-lactate is the end product of anaerobic glycolysis. During this process it is formed out of pyruvic acid by the enzyme lactate dehydrogenase (LDH). During ischaemia and also intestinal ischaemia, the cells will start anaerobic dissimilation and the serum lactate rises.[6] Next, L-lactate is absorbed, mostly by the liver but partially by the kidney. There it is converted back to pyruvate and by gluconeogenesis to glucose. Thus, an increased serum L-lactate can be a result of tissue hypoperfusion, as well as a decreased lactate metabolism in the liver or kidney. Furthermore various other medical conditions are associated with an increase in serum L-lactate, such as diabetic keto-acidosis and malignancy.[6] Experimental studies have shown that the liver is able to increase lactate uptake in case of excessive mesenteric lactate production so that an increased serum L-lactate can be compensated.[7]
D-lactate is an isomer of lactate that is not produced by the human body, but released by intestinal bacteria. Increased serum D-lactate during intestinal ischaemia might be caused by bacterial overgrowth of these bacteria.[6] The D-isomer is metabolised by a D-LDH enzyme.[6] In daily care, lactate measurement includes L-lactate, which is measured by using an enzymatic reaction between L-lactate and either L-lactate oxidase or L-LDH. Both of these enzymes are specific for L-lactate. Therefore, D-lactate is not routinely obtained when measuring

L-lactate. D-lactate is measured by using an enzymatic reaction with D-LDH, which is not available in most hospitals.
The goal of this review is to assess the diagnostic value of serum L-Lactate and D-lactate measurement in acute mesenteric ischaemia, and thereby ascertain whether or not these should be used in daily practice.

METHODS

To find available literature on serum lactate measurement we performed a literature search in PubMed, Cochrane and Embase with the search terms lactate, lactic acid, marker, mesenteric, intestinal, bowel, colon, colitis, ischaemic, ischaemia, infarction and their corresponding MeSH terms. The search was limited to English full-text articles conducted in humans. Results of the search are shown in *figure 1*.
Studies, (systematic) reviews or meta-analyses about the diagnostic value of lactate or multiple biomarkers including lactate were included. Exclusion criteria were case reports and articles about mesenteric ischaemia after a specific type of surgery. To find additional literature not discussed in reviews or not found by the search, Web of Science was used for a cross-reference search. We found 358 unique articles, which were screened on title and abstract. Eleven full-text articles were assessed for their eligibility, of which two articles were excluded as they only compared absolute values of lactate between patients with and without AMI, and did not assess the diagnostic value.

Figure 1. *Flowchart of the literature search*



If the sensitivity or specificity of the test was not given and sufficient data were available, we calculated these parameters according to standard methods.

RESULTS

L-lactate in acute mesenteric ischaemia

In a review in 2012, Demir et al.[6] described six relatively small studies on the diagnostic value of L-lactate for acute mesenteric ischaemia, with variable results (*table 1*).[8-14] The three oldest studies show a high sensitivity for acute

Table 1. *Diagnostic value of L-lactate for acute mesenteric ischaemia*

Study	Design	Results	Conclusion
Lange 1994[8]	Prospective, patients with acute abdominal symptoms, n = 85	Serum L-lactate before diagnosis or preoperatively increased in all patients with MI (n = 20), but also in many other patients	**Sensitivity 100%** **Specificity 42%**
Meyer 1998[9]	Retrospective, patients operated for AMI, n = 46	Serum L-lactate preoperatively increased in > 90%* of patients with AMI. Only 19 patients operated < 6 hours, 12 > 24 hours after presentation	**Sensitivity > 90%***
Lange 1997[10]	Prospective, patients with abdominal pain, n = 120	Serum L-lactate increased in 24 of 25 patients with MI, but also in many other patients	**Sensitivity 96%** **Specificity 36%**
Gearhart 2003[11]	Prospective, patients clinically suspected for AMI, n = 58	Serum L-lactate increased in 24 of 31 patients with AMI, 8 false-positively increased	**Sensitivity 78%** **Specificity 53%**
Cronk 2006[12]	Prospective, patients admitted for mechanic bowel obstruction, n = 21	Serum L-lactate increased in 1 of 3 patients with gut necrosis, 5 false-positively increased	**Sensitivity 33%** **Specificity 72%**
Acosta 2012[13]	Retrospective, patients with AMI, n = 55	Serum L-Lactate increased in 14 of 27 patients (other patients had no L-lactate measurement)	**Sensitivity 52%**
Van der Voort 2014[14]	Prospective, patients on ICU clinically suspected of AMI, n = 44	Serum L-lactate increased in 18 of 23 patients with AMI	**Sensitivity 78%** **Specificity 48%**

N = number of patients; (A)MI= (acute) mesenteric ischaemia; ICU = Intensive Care Unit. *Not further specified

mesenteric ischaemia of over 90%, whereas the three more recent studies show a low to moderate sensitivity (total range sensitivity 33%-100%). For several reasons, these results should be interpreted with caution. First, in two of the three studies with a high sensitivity, lactate was partially obtained preoperatively and not during initial evaluation while in some cases there was a significant time interval between initial evaluation and surgery.[8,9] In the study conducted by Lange et al.[8] sensitivity was 100%, but the median symptom duration was 43 hours and the postoperative 30-day mortality was 90%. Second, two of the three studies reporting a high sensitivity may have an overlap in patient cohort as both were conducted by the same author.[8,10] One of the three studies with low sensitivity included patients with mechanical bowel obstruction, and only three patients with gut necrosis.[12] Since two of the six studies included patients with AMI retrospectively, the specificity was not calculated in these studies. In the remaining four studies there was a low specificity (range 36%-72%). In view of these data, the use of serum L-lactate measurement in our opinion appears to be unfit for the diagnosis of AMI since in general it has a low specificity and a moderate sensitivity.

The prognostic value of L-lactate in intestinal ischaemia

Although the usefulness of L-lactate as a diagnostic marker is limited, it still might have a prognostic value. In a retrospective French study of patients with AMI admitted to the intensive care unit (ICU), a serum L-lactate > 2.7 mmol/l gave an odds ratio (OR) for ICU mortality of 2.36 (95% CI 1.52-3.66) in a multivariable analysis.[15] A similar result was found in another study with patients operated for AMI, where the mortality was significantly increased in patients with a serum L-lactate above 2.0 mmol/l ($p < 0.002$, no OR, univariate analysis).[16] These studies show that an increased serum L-lactate appears to be an unfavourable prognostic sign rather than a diagnostic marker for AMI.

D-lactate in acute mesenteric ischaemia

A systematic review by Evenett et al.[4] discussed multiple serological markers for intestinal ischaemia and included a review of four studies on D-lactate. Since two of those four studies were conducted in patients after aorta surgery, we do not present these. In the two other studies, D-lactate was measured prospectively in patients with acute abdominal complaints (*table 2*). One of the studies obtained the D-lactate preoperatively. This study found a high sensitivity and specificity. The other study, which measured D-Lactate at presentation of symptoms, showed a high sensitivity but a very low specificity of 23%.[17,18] In a comparable cohort from a recent Chinese prospective trial, sensitivity was moderate at 67% but specificity was high (86%).[19] Although D-lactate appears to be a little bit more reliable than L-lactate as a diagnostic marker for AMI, its performance in the current literature is still not good enough to be used in daily practice.

DISCUSSION

Acute mesenteric ischaemia is a rapidly progressive disease with high mortality. Whereas the current European Society of Vascular Surgery (ESVS) guideline for vascular mesenteric disease advises to perform CT angiography in patients with high clinical suspicion,[20] L-lactate is often incorporated in the diagnostic work-up in daily clinical practice. Obviously, the need for a reliable biomarker is high, as it can increase clinical suspicion for AMI and thus reduce delay.[1] The routinely measured serum L-lactate, however, does not seem to be the appropriate candidate. Although the sensitivity of the test was high in some older studies, these studies had severe methodological limitations.[8-10] Newer studies found a much lower sensitivity, making serum L-lactate an unfit test in ruling out AMI.[11-14] Moreover, all studies found a low to moderate specificity, corresponding to the fact that there are many other causes for a high serum L-lactate. In our opinion, L-lactate should not be used to diagnose or rule out acute occlusive mesenteric ischaemia. This view is shared by the recent ESVS guideline for vascular mesenteric disease.[20] While the diagnostic value of L-lactate is limited, other studies showed that it might have a role as a prognostic marker, since patients with a high serum L-lactate

Table 2. *Diagnostic value of D-lactate for acute mesenteric ischaemia*

Study	Design	Results	Conclusion
Murray 1994[17]	Prospective, patients with acute abdominal complaints, n = 31	Serum D-lactate preoperatively increased in 8 of 9 patients with AMI, 3 false-positive results	**Sensitivity 89%** **Specificity 86%**
Block 2008[18]	Prospective, patients with acute abdominal complaints, n = 71	Serum D-lactate increased in 8 of 9 patients with MI, 47 false-positive results	**Sensitivity 90%** **Specificity 23%**
Shi 2015[19]	Prospective, patients with abdominal pain requiring surgery, n = 272	Serum D-lactate increased in 26 of 39 patients with MI	**Sensitivity 67%** **Specificity 86%**

N = number of patients; (A)MI: (acute) mesenteric ischaemia.

demonstrate an increased mortality rate. The most probable explanation seems to be that an increased serum L-lactate in AMI reflects advanced AMI.[15,16]

The sparingly measured isomer D-lactate also appears to be too unreliable for the diagnosis of AMI. A study where serum D-lactate was obtained preoperatively showed promising results, but the studies where serum D-lactate was obtained at initial presentation of the patient did not demonstrate added value of the test.[17-19] Possible explanations for the limited value, despite the exclusive intestinal origin of D-lactate, are that increased serum D-lactate values are also found in people with a high carbohydrate intake, people who use probiotics and those who have decreased colon motility.[6] Other studies have found that serum D-lactate levels are elevated in people who have had a jejunoileal bypass operation or who have the short-bowel syndrome.[17]

Although serum D-lactate in general performed slightly better than serum L-lactate, the results are inconsistent. Moreover, there were not many studies investigating D-lactate and regrettably not a single study compared serum D- and L-lactate in a single study population. Although Van der Voort et al.[14] looked at both tests in their ICU study, they only presented absolute values for D-lactate and no sensitivity or specificity. It is therefore impossible to compare the diagnostic performance of the two isomers in this study group.

Though not readily available in daily practice, the measurement of intestinal fatty-acid binding proteins (i-FABP) might have diagnostic value in intestinal ischaemia. These proteins are located in the enterocyte and help with the transport of fatty acids over the cell membrane. When mucosal damage occurs, these proteins enter the circulation and are detectable.[5,19,21,22] Multiple prospective trials have recently been conducted to assess the diagnostic value of i-FABP in mesenteric ischaemia. In a meta-analysis published in 2016 the results of the diagnostic value of i-FABP from nine studies were pooled, resulting in a pooled sensitivity of 0.80 (95% CI: 0.72-0.86) and a pooled specificity of 0.85 (95% CI: 0.73-0.93).[21]

In the three biggest trials, especially the negative predictive value (NPV) stood out. Although the NPV is specific for a certain patient population and not for the test itself, it was remarkably high in all three populations. In a Japanese trial where small bowel ischaemia was found 52 times in 361 patients with acute abdomen, the NPV of i-FABP was 95%.[22] An NPV of 96% was found in a Chinese trial with 272 patients with abdominal pain requiring surgery where 39 had mesenteric ischaemia.[19] Another Japanese trial where 24 cases of AMI were found in 208 patients clinically suspected for AMI, showed an NPV of 98%.[5] The positive predictive value (PPV) of the serum i-FABP test was very low in these studies, 32%, 33% and 50%, respectively.[5,19,22] Thus, although the potential to diagnose AMI is very limited, it might be very useful in virtually excluding the diagnosis of AMI. Currently an ELISA method is used for the serum i-FABP measurement. Since this test takes three to four hours, its clinical use is limited.[19,22] However, Kanda et al.[22] report that they are developing a faster test (< 1 hour). Although, in the currently available literature, the D-dimer test too has a very poor specificity,[4] the sensitivity is around 95% in multiple studies.[20] The ESVS therefore now recommends a D-dimer test to exclude AMI in patients with acute abdominal pain.[20]

Besides the two isomers of lactate and i-FABP, many other biomarkers were also investigated for their diagnostic value regarding AMI. For instance, creatine kinase, leukocyte count, C-reactive protein and LDH showed inferior results compared with lactate.[4,19] Multiple reasons have been put forward in the literature as to why finding a reliable biomarker for intestinal ischaemia appears to be this hard. First, the release of intestinal proteins into circulation might not start until severe mucosal damage has occurred. Second, the blood collected in the intestine passes the liver first, which might prevent these proteins from entering the systemic circulation.[17] Finally, non-occlusive mesenteric ischaemia is often present in ICU patients.[23] These patients are often included as control group in studies assessing biomarkers for AMI, which obviously hampers the discriminative power as a marker of AMI.

CONCLUSION

Acute mesenteric ischaemia (AMI) is a life-threatening disease with a mortality rate around 60%. This high mortality rate is largely caused by diagnostic delay. Diagnosis is made by CT angiography with a slice thickness of 1 mm or thinner. A reliable biomarker is needed for early diagnosis and for the ability to correctly assess a patient's likelihood of ischaemia to increase clinical suspicion and thereby reduce delay. Although frequently measured in daily practice, as part of the diagnostic work up, L-lactate appears to be unsuitable to be used due to its low specificity and moderate sensitivity. Instead, an increased serum L-lactate in AMI is in general an unfavourable prognostic sign indicating an increase of mortality risk.

DISCLOSURES

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REFERENCES

1. Adaba F, Askari A, Dastur J, et al. Mortality after acute primary mesenteric infarction: a systematic review and meta-analysis of observational studies. Colorectal Dis. 2015;17:566-77.
2. Oldenburg W, Lau L, Rodenberg T, Edmonds H, Burger C. Acute mesenteric ischemia: a clinical review. Arch Intern Med. 2004;164:1054-62.
3. Kougias P, Lau D, El Sayed H, et al. Determinants of mortality and treatment outcome following surgical interventions for acute mesenteric ischemia. J Vasc Surg. 2007;46:467-74.
4. Evenett N, Petrov M, Mittal A, Windsor JA. Systematic review and pooled estimates for the diagnostic accuracy of serological markers for intestinal ischemia. World J Surg. 2009;33:1374-83.
5. Matsumoto S, Sekine K, Funaoka H, et al. Diagnostic performance of plasma biomarkers in patients with acute intestinal ischemia. Br J Surg. 2014;101:232-8.
6. Demir I, Ceyhan G, Friess H. Beyond Lactate: Is There a Role for serum lactate measurement in diagnosing acute mesenteric ischemia? Dig Surg. 2012;29:226-35.
7. Jakob S, Merasto-Minkkinen M, Tenhunen J, et al. Prevention of systemic hyperlactatemia during splanchnic ischemia. Shock. 2000;14:123-7.
8. Lange H, Jäckel R. Usefulness of plasma lactate concentration in the diagnosis of acute abdominal disease. Eur J Surg. 1994;160:381-4.
9. Meyer T, Klein P, Schweiger H, Lang W. How can the prognosis of acute mesenteric artery ischemia be improved? Results of a retrospective analysis (in German). Zentralbl Chir. 1998;123:230-4.
10. Lange H, Toivolo A. Warning signals in acute abdominal disorders. Lactate is the best marker of mesenteric ischemia (in Swedish). Lakartidningen. 1997;94:1893-6.
11. Gearhart S, Delaney C, Senagore A, et al. Prospective assessment of the predictive value of alpha-glutathione S-transferase for intestinal ischemia. Am Surg. 2003;69:324-9.
12. Cronk D, Houseworth T, Cuadrado D, et al. Intestinal fatty acid binding protein (I-FABP) for the detection of strangulated mechanical small bowel obstruction. Curr Surg. 2006;63:322-5.
13. Acosta S, Block T, Björnsson S, et al. Diagnostic pitfalls at admission in patients with acute superior mesenteric artery occlusion. J Emerg Med. 2012;42:635-41.
14. Van der Voort P, Westra B, Wester J, et al. Can serum L-lactate, D-lactate, creatine kinase and I-FABP be used as diagnostic markers in critically ill patients suspected for bowel ischemia. BMC Anesthesiol. 2014;14:111.
15. Leone M, Bechis C, Baumstarck K, et al. Outcome of acute mesenteric ischemia in the intensive care unit: a retrospective, multicenter study of 780 cases. Intensive Care Med. 2015;41:667-76.
16. Ritz JP, Germer CT, Buhr HJ. Prognostic factors for mesenteric infarction: multivariate analysis of 187 patients with regard to patient age. Ann Vasc Surg. 2005;19:328-34.
17. Murray MJ, Gonze MD, Nowak LR, et al. Serum D(–)-lactate levels as an aid to diagnosing acute intestinal ischemia. Am J Surg. 1994;167:575-8.
18. Block T, Nilsson TK, Bjorck M, et al. Diagnostic accuracy of plasma biomarkers for intestinal ischemia. Scand J Clin Lab Invest. 2008;68:242-8.
19. Shi H, Wu B, Wan J, Liu W, Su B. The role of serum intestinal fatty acid binding protein levels and D-lactate levels in the diagnosis of acute intestinal ischemia. Clin Res Hepatol Gastroenterol. 2015;39:373-8.
20. Bjorck M, Koelemay M, Acosta S, et al. Editor's Choice – Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2017;53:460-510.
21. Sun D, Cen Y, Li S, et al. Accuracy of the serum intestinal fatty-acid-binding protein for diagnosis of acute intestinal ischemia: a meta-analysis. Sci Rep. 2016;6:34371.
22. Kanda T, Tsukahara A, Ueki K, et al. Diagnosis of ischemic small bowel disease by measurement of serum intestinal fatty acid-binding protein in patients with acute abdomen: a multicenter, observer-blinded validation study. J Gastroenterol. 2011;46:492-500.
23. Kolkman JJ, Mensink PB. Non-occlusive mesenteric ischemia: a common disorder in gastroenterology and intensive care. Best Pract Res Clin Gastroenterol. 2003;17:457-73.

ORIGINAL ARTICLE

Type 2 diabetes mellitus severity correlates with risk of hip fracture in patients with osteoporosis

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ABSTRACT

Background: Osteoporosis is a major public health problem because of its associated fractures and the resulting complications. The objective of this study was to identify the association between the severity of type 2 diabetes mellitus (T2DM) and the risk of hip fracture in osteoporotic patients.

Methods: The patients who received a diagnosis of osteoporosis between 2006 and 2010, with an adequate follow-up between 2006 and 2015, were enrolled in this study. Among patients with T2DM, the severity of the disease was evaluated using the Diabetes Complication Severity Index (DCSI). Logistic regression models were used to calculate the odds ratios and to predict the risk of hip fracture in diabetic osteoporotic patients.

Results: A total of 1188 patients were enrolled in the final study, 87 patients had hip fractures in the follow-up period between 2006 and 2015. Among the diabetic patients, each level of the continuous DCSI was associated with a 1.56-fold greater risk of hip fracture. In further stratification, patients with a DCSI > 3 had a significantly higher risk of hip fracture in comparison with those with a DCSI ≤ 1. The categorical DCSI (DCSI > 3), Hb_{A1c} level on the diagnosis of T2DM and duration of diabetes, facilitate predicting the risk of hip fracture.

Conclusion: The severity of T2DM reflects the risk of hip fracture in osteoporotic patients. Physicians should pay attention to osteoporotic patients presenting with a high Hb_{A1c} level on diagnosis of T2DM and a higher DCSI because of their vulnerability to hip fracture.

KEYWORDS

Osteoporosis, type 2 diabetes mellitus (T2DM), hip fracture, diabetes complications severity index (DCSI)

INTRODUCTION

Osteoporosis is a bone condition defined by low bone mass, decreased bone quality or increased fragility, and increased fracture risk.[1,2] It is a major public health problem because of its associated fractures and the resulting complications, including mortality. Therefore, identifying populations at risk of osteoporosis and fracture is critical for the prevention of the disease and further intervention. Many risk factors for osteoporosis have been identified, such as age, being post-menopausal, currently smoking, and excessive intake of alcohol, which were incorporated into the Fracture Risk Assessment Tool (FRAX) developed by the World Health Organisation. Nevertheless, diabetes may be an overlooked a risk factor despite substantial evidence indicating that type 2 diabetes mellitus (T2DM) is associated with a higher risk of hip fracture, independent of sex, increased body mass index, or other classical risk factors of osteoporosis.[3-6] In addition, while bone mineral density plays a major role in the current risk assessment tool, current evidence reveals a discrepancy in fracture risk and bone mineral density in patients with T2DM.[7] Most studies have shown increased bone mineral density in T2DM patients;[8,9] however, the risk of fracture is still higher compared with that of non-diabetic patients.

FRAX, as the most widely used risk assessment tool for osteoporosis, may therefore underestimate the risk of fracture in diabetic patients.[10,11]

Considering underestimation of fracture risk in diabetic osteoporotic patients, we highlight the correlation between T2DM and osteoporotic fractures. Furthermore, while the relation between T2DM and osteoporosis has been widely examined in previous studies, no study has addressed whether the severity of T2DM affects the risk of fracture in patients with osteoporosis. To identify the population at risk of hip fracture, we conducted a retrospective study of osteoporotic patients aged over 40 years in a regional hospital in central Taiwan. In this study, we try to identify possible risk factors for hip fracture, and examine the correlation between the severity of T2DM and risk of hip fracture in patients with osteoporosis.

MATERIALS AND METHODS

Study design and subjects

This was a retrospective study. The data were obtained from the database of Puli Christian Hospital, a regional hospital in central Taiwan. The database contains information such as patient profiles (date of birth, sex, ethnicity), inpatient and outpatient records, laboratory data, examination results, and all previous diagnoses classified according to the International Classification of Diseases, Ninth Revision (ICD-9). The data, such as patient profiles, inpatient and outpatient diagnoses, and records of prescription use, are sent to the Bureau of National Health Insurance (NHI) for reimbursement purposes, and further incorporated into the research database of the NHI, which has often been used in high-quality epidemiological research in Taiwan.

By using the ICD-9 codes, we identified patients who received a diagnosis of osteoporosis between 2006 and 2010. Participants were selected based on the following criteria: 1) age greater than 40 years, 2) diagnosis of osteoporosis (ICD-9 code 733.0) in 2006-2010, and 3) at least three visits to the outpatient department or one admission[12] between 2006 and 2015. Samples were excluded because of 1) death not related to hip fracture during the follow-up period of 2006-2015, 2) insufficient follow-up, 3) referrals from other hospitals, and 4) hip fracture before the diagnosis of osteoporosis or T2DM. Information including the duration of diabetes, Hb_{A1c} (measured on the diagnosis of T2DM), and previous medical history was obtained by reviewing patients' medical records. Any event of hip fracture occurring between 2006 and 2015 was considered in the outcome of this research.

Evaluation of diabetes severity: Diabetes Complications Severity Index

The severity of the diabetes of all the patients was graded according to the Diabetes Complication Severity Index (DCSI). The DCSI was developed by Young et al.[13] in 2008 and it comprises seven categories of diabetes complications: cardiovascular disease, nephropathy, peripheral vascular disease, cerebrovascular events, neuropathy, retinopathy, and metabolic complications. The DCSI was developed to model the severity of diabetes complications at any point in time. Except for neuropathy, which is categorised into only two levels (0 and 1), all other complications can be graded in three levels (0, 1, and 2) based on the severity. Therefore, a total score of 13 is possible for the DCSI, with a minimum of 0. In our study, all patients with T2DM were stratified according to the DCSI to highlight the correlation between the severity of diabetes and the risk of hip fracture in osteoporotic patients.

Statistical analysis

The *t*-test and chi-square test were used to compare the baseline characteristics between 1) the hip fracture group and the non-fracture group, and 2) groups of patients with T2DM stratified according to the DCSI. A logistic regression model was used to examine the relationship between the severity of diabetes complications and the risk of hip fracture in the osteoporotic patients. Odds ratios (ORs) were calculated through both univariate analysis and multivariate logistic regression; in the multivariate analysis, other possible confounding variables were adjusted for.

Osteoporotic patients with T2DM were stratified according to the DCSI. Stepwise model selection for the series of model comparisons was used to identify the most effective predictive markers for the risk of fracture in patients with osteoporosis. In addition, c-statistics (area under the curve, AUC) were introduced to determine whether grouped stratification of the DCSI (i.e., DCSI 0-1, DCSI 2-3, DCSI > 3) was more effective in predicting fracture than linearisation or simple count categorisation of the DCSI. By using this method, we intended to determine a cut-off point of the DCSI for intervention purposes in patients with osteoporosis.

RESULTS

A total of 1244 patients were recruited by reviewing the patients' medical records between 2006 and 2010. Among the 1244 patients, 56 were excluded for the following

reasons: death not related to hip fracture (24), insufficient follow-up (27), and referrals from other hospitals (5). A total of 1188 patients were considered eligible for final analysis. Of these 1188 patients, 87 had hip fractures during the follow-up period.

Comparing the baseline characteristics between the hip fracture group and the non-fracture group (*table 1*) revealed that the patients who had fractures were significantly older, with a mean age of 76.1 years in comparison with 70.9 years ($p < 0.001$). Among those with hip fractures, the prevalence of T2DM was significantly higher at 17.2% compared with 8.4% ($p = 0.005$). Other variables including sex, ethnicity (Han Chinese, aboriginal, others), presence of COPD, hypertension, and rheumatoid arthritis were not associated with a significant difference in the prevalence between the two groups. This observation suggests that T2DM is a risk factor for hip fracture in patients with osteoporosis.

Among all patients with osteoporosis, 107 previously received a diagnosis of T2DM. Of the patients with T2DM, 43 (40.2%) had a DCSI of 0-1, 35 (32.7%) had a DCSI of 2-3, and 29 (27.1%) had a DCSI > 3 (*table 2*). One-way ANOVA for comparing the baseline characteristics revealed a significant difference in the mean duration of diabetes between the groups. Post hoc tests showed a significant difference between the DCSI 0-1 group and the DCSI > 3 group ($p < 0.05$). The patients with a higher DCSI tended to be older and have a higher Hb_{A1c} level on diagnosis of T2DM.

Of the 107 diabetic osteoporotic patients, 15 suffered hip fractures. The adjusted OR of hip fracture is shown in *table 3*. Both univariate and multivariate analyses using logistic regression were performed. When the DCSI was considered a linear variable, the OR was 1.56 (95% confidence interval [CI] = 1.12-2.12) in univariate analysis, and it was 1.89 (95% CI = 1.21-2.95) in multivariate analysis after adjustment for age, duration of diabetes, Hb_{A1c} on diagnosis of T2DM, presence of COPD, and hypertension. When the linear form of the DCSI was replaced with the categorical DCSI, a significant trend of increasing risk in patients with higher diabetes complication severity was noted (Cochran-Armitage trend test, $p < 0.05$). When the patients were divided into three categories according to the DCSI severity, the DCSI > 3 group had a significantly higher risk compared with the DCSI 0-1 group (OR = 7.81, 95% CI = 1.52-40.11 in univariate analysis; adjusted OR =28.65, 95% CI = 2.46-334.17 in multivariate analysis).

By using stepwise model selection, models were established for a categorical variable (DCSI 0-1, DCSI 2-3, and DCSI > 3) and a linear variable of the DCSI. The model with the categorical DCSI contained two other variables, the duration of diabetes and Hb_{A1c} level on diagnosis (*table 4*); in the other model, the linear DCSI was the only variable that was associated with a significant difference in fracture risk. For model comparison, we established receiver operating characteristic (ROC) curves of both models: the AUC was 0.7462 for the model with the linear DCSI, and the AUC was 0.8346 for the model with the categorical DCSI, with the difference being significant ($p = 0.029$) (*figure 1*). This result suggests that the model containing the categorical DCSI is slightly more effective in predicting hip fracture risk in patients with osteoporosis with T2DM.

Table 1. *The characteristics of non-hip fracture and hip fracture groups*

	Non-hip fracture	Hip fracture	p-value
Total (n)	1101	87	
Mean age, years (SD)	70.9 (12.4)	76.1 (11.9)	< 0.001
Sex			0.498
- Male (n, %)	228 (20.7%)	17 (19.5%)	
- Female (n, %)	1073 (79.3%)	70 (80.5%)	
T2DM (n, %)	92 (8.4%)	15 (17.2%)	0.005
Race			0.848
- Han Chinese (n, %)	996 (90.5%)	76 (87.4%)	
- Aboriginals (n, %)	68 (6.2%)	10 (11.5%)	
- Others (n, %)	37 (3.4%)	1 (1.2%)	
Hypertension (n, %)	88 (8.0%)	9 (10.3%)	0.441
COPD (n, %)	128 (11.6%)	7 (8.1%)	0.311
Rheumatoid arthritis (n, %)	35 (3.2%)	0	

DISCUSSION

This was the first retrospective study to determine whether diabetes severity is associated with the risk of hip fracture in osteoporotic patients. The results of this study not only confirm that T2DM is a risk factor for hip fracture but also indicate that patients with greater diabetes severity are at a higher risk of hip fracture. In addition, in the predictive model selected for our study, three predictors associated with hip fracture in osteoporotic patients were identified: the severity of diabetes, Hb_{A1c} level on diagnosis of T2DM, and the duration of diabetes.

Table 2. *The characteristics of stratified groups according to the DCSI*

	DCSI: 0-1	DCSI: 2-3	DCSI: > 3	p-value
Total (n)	43	35	29	
Age (mean, SD)	70.4 (10.0)	72.1 (9.1)	75.4 (7.6)	0.081
Mean duration of T2DM (years, SD)	6.6 (3.0)	8.2 (3.4)	8.6 (3.2)	0.018
Hb_{A1c} (measured at diagnosis of T2DM) (SD)	7.69 (1.6)	8.08 (1.4)	8.2 (1.5)	0.359
Alanine aminotransferase (SD)	28.4 (33.2)	30.3 (27.2)	30.3 (22.1)	0.947
Male (n, %)	10 (23.3%)	9 (25.7%)	9 (31.0%)	0.766
Race				0.133
- Han Chinese (n, %)	37 (86.0%)	35 (100.0%)	27 (93.1%)	
- Aboriginals (n, %)	6 (14.0%)	0	1 (3.5%)	
- Others (n, %)	0	0	1 (3.5%)	
Hypertension (n, %)	5 (11.6%)	9 (25.7%)	7 (24.1%)	0.235
COPD (n, %)	9 (20.9%)	7 (20.0%)	4 (13.8%)	0.732
Rheumatoid arthritis (n, %)	0	0	1 (3.5%)	0.263

Table 3. *Multivariate analysis of hip fracture risk by using logistic regression*

	Unadjusted odds ratio	95% CI	Adjusted odds ratio	95% CI
Mean age	0.99	0.94, 1.05	0.97	0.89, 1.07
Duration of T2DM	0.95	0.80, 1.12	0.86	0.68, 1.10
Hb_{A1c} (measured on diagnosis of T2DM)	1.52	1.04, 2.22	1.70	0.99, 2.89
Male	0.67	0.21, 2.12	0.49	0.10, 2.43
Present hypertension	0.59	0.12, 2.85	0.33	0.03, 3.59
COPD	1.10	0.28, 4.34	1.68	0.34, 8.35
DCSI (linear)	1.56*	1.12, 2.12	1.89*	1.21, 2.95
DCSI (categorical)				
Cochran-Armitage trend test ($p < 0.05$)				
0	Reference		Reference	
1	1.05	0.06, 17.95	1.89	0.08, 45.16
2	3.23	0.27, 39.29	6.23	0.29, 135.15
3	3.71	0.35, 38.93	8.08	0.42, 155.30
4	6.30	0.58, 68.42	17.38	0.77, 393.25
5+	9.55	0.99, 92.17	17.43	0.78, 392.22
DCSI (categorical)				
0-1	Reference		Reference	
2-3	3.42	0.62, 18.82	9.73	0.96, 98.32
> 3	7.81*	1.52, 40.11	28.65*	2.46, 334.17

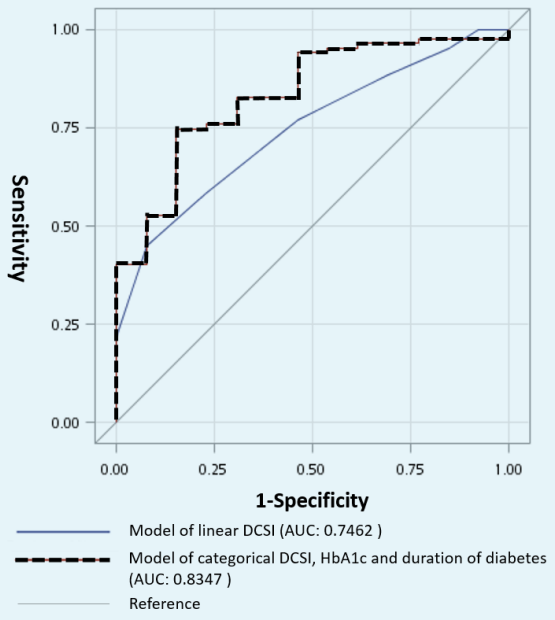
* p-value < 0.05.

Table 4. *Predictive models selected by stepwise model selection using categorical DCSI*

Predictors	Odds ratio (OR)	95% CI
Duration of T2DM	0.80	0.64, 0.99
Hb_{A1c} on diagnosis	1.66	1.02, 2.68
DCSI		
0-1	Reference	Reference
2-3	2.29*	1.01, 97.83
> 3	3.06*	2.19, 210.54
Area under curve (AUC) = 0.8347		

*p-value < 0.05.

Figure 1. *Receiver operating characteristics (ROC) curves comparing model with linear DCSI and with categorical DCSI (DCSI 0-1, DCSI 2-3, DCSI > 3), the area under curve (AUC) of categorical DCSI is 0.8347, whereas the AUC of linear DCSI is 0.7462, with statistical significant difference (p = 0.029)*



T2DM in osteoporosis

Several mechanisms have been proposed to explain the relationship between diabetes or hyperglycaemia and osteoporosis. T2DM is associated with increased bone mineral density[8-9,14] and an increased risk of fracture.[7,15] The early studies attributed the increased fracture risk to the use of thiazolidinedione[16] or insulin[17] and the increased frequency of falling to diabetes complications.[18] A study reported that diabetes complications, such as autonomic neuropathy, peripheral neuropathy, retinopathy, and syncope related to hypoglycaemia, are associated with an increased frequency of falling.[19] However, when the frequency of falling is controlled for, T2DM still remains an independent risk factor for fracture.[3,20] Additionally, the observation periods of many studies included the time period prior to the widespread use of thiazolidinedione;[21] thus, the use of thiazolidinedione may not fully account for the increased risk of fracture in T2DM patients. Recently studies have suggested that some bone properties (e.g., alterations in the trabecular compartment of bone,[22] micro-architectural deficits,[23] accumulation of advanced glycation end products[24,25]) that are undetectable through bone densitometry also contribute to the risk of fracture in diabetic patients.

Although the mechanism of the increased risk of fracture in T2DM is not yet fully understood, it should be noted that T2DM has implications for bone strength in multiple aspects. In addition to fall frequency, skeletal resorption and mineralisation defects are associated with hyperparathyroidism related to renal dysfunction, a common complication of T2DM.[26] The microvascular disease related to T2DM may interfere with blood flow to the bone marrow, thus affecting the microenvironment and local remodelling of the bone.[27,28] While the DCSI provides a general impression of diabetes severity and has been validated in predicting adverse outcomes of T2DM,[13,29] it may also be valuable in assessing bone complications. Our study established that a higher severity of diabetes is associated with an increased risk of hip fracture. This information may assist in early identification of a high-risk group of osteoporotic patients with T2DM.

Duration of T2DM and the role of Hb_{A1c} in risk assessment

In the predictive model selected, when the Hb_{A1c} level and a high DCSI were considered risk factors, the duration of diabetes served as a mildly protective factor in the diabetic osteoporotic patients. We reviewed the duration of diabetes in those who suffered hip fractures, and the data showed a mean duration of 5.7 years in the DCSI 0-1 group, 8.01 years in the DCSI 2-3 group, and 7.0 years in the DCSI > 3 group. The Hb_{A1c} measured on diagnosis was 7.8 in the DCSI 0-1 group, 8.8 in the DCSI 2-3 group, and 9.0 in the DCSI > 3 group. The data revealed that, in our study, osteoporotic patients with diabetes who are at risk of hip fracture tend to have a shorter diabetes duration, a higher Hb_{A1c} level on diagnosis, and higher diabetes severity. A possible explanation is that the patients recruited in our study who later developed hip fracture did not receive a

diagnosis at the onset of diabetes and generally presented with a higher Hb_{A1c} on diagnosis. Since our hospital is located in the mountainous area of central Taiwan, where many aboriginal tribes reside, medical accessibility may not be similar to urban areas due to inconvenience of transportation.[30]

According to the American Diabetes Association, undiagnosed diabetes is not uncommon, with as many as 27.8% of diabetic patients not receiving a diagnosis.[31] Since it may be difficult to determine the actual onset of diabetes, Hb_{A1c} screening may therefore have value not only in diagnosing diabetes but also as a predictive marker for complications. A previous study reported that the pre-intervention Hb_{A1c} is significantly associated with the risk of complications such as diabetic retinopathy, and is associated with an increased risk of fracture.[32] In addition, a study confirmed that long-standing glycaemic exposure (with a threshold of the mean $Hb_{A1c} \geq 6.5$) increases the risks of vascular complications and death,[33] which also suggests that Hb_{A1c} is valuable in predicting the risk of future complications.

In our study, instead of using the mean Hb_{A1c} in the analysis, we employed the Hb_{A1c} value on diagnosis of T2DM. This is because the increasing awareness of 'metabolic memory' has suggested that diabetic stresses persist despite glucose normalisation.[34] Based on the theories, recent studies have indicated that intensive glucose control offers no protection against cardiovascular risk and mortality in T2DM.[35,36] A study reported that the prevalence of osteoporosis and frequency of fractures were higher in long-standing T2DM, irrespective of blood glucose control.[37] While bone tissue may be one of the memory's target organs, the mean Hb_{A1c} may be of less value in risk assessment compared with the Hb_{A1c} level on the onset of the disease. In our study, we established that the Hb_{A1c} level on diagnosis of T2DM is associated with a greater risk of hip fracture and therefore may be useful for predicting bone complications.

To conclude, patients who later had hip fractures during follow-up generally presented with a higher Hb_{A1c} level on diagnosis of T2DM and a higher severity of disease, which may serve as surrogate predictors in addition to the current screening tools for early prediction in osteoporotic patients, particularly because FRAX may underestimate the risk of fracture in diabetic patients.[7,8]

Limitations

This was a retrospective study with ICD-9 coding from the database, and it has several limitations. First, the patients were enrolled based on the clinical diagnosis of osteoporosis during the follow-up period, and the severity of osteoporosis or the extent of hip fracture could not be assessed. Second, the diagnosis of osteoporosis and diabetes was made by different physicians with different methods or criteria. However, the National Health Insurance program of Taiwan was implemented in 1995, and most Taiwanese were covered by this insurance. All insurance claims should be scrutinised by medical reimbursement specialists. Although osteoporosis was diagnosed by individual physicians who may define the condition using different methods, such as dual-energy X-ray absorptiometry or quantitative ultrasound, the diagnoses in this study were highly reliable. Similarly, the diagnosis of diabetes was made by either Hb_{A1c} or fasting glucose, depending on the specialist. Third, although we could review certain baseline characteristics of the participants in our study, information regarding patients' lifestyles (e.g., amount of alcohol intake and smoking) is lacking in the database. Finally, we used the DCSI to evaluate the severity of T2DM; the DCSI is an unweighted index which does not independently test adverse outcomes associated with each complication.[11]

Although this study has several limitations, it realistically reflects the relationship between the severity of T2DM and risk of hip fracture in osteoporotic patients.

CONCLUSION

The severity of T2DM is associated with an increased risk of hip fracture in osteoporotic patients. The categorical DCSI (DCSI > 3), Hb_{A1c} level on diagnosis of T2DM and duration of diabetes facilitate predicting the risk of hip fracture. Physicians should pay attention to osteoporotic patients presenting with a high Hb_{A1c} level on diagnosis of T2DM and a higher DCSI because of their vulnerability to hip fracture.

DISCLOSURES

The authors declare no conflict of interest.

REFERENCES

1. Ensrud KE, Crandall CJ. Osteoporosis. Ann Intern Med. 2017;167:ITC17-32.
2. Rubin MR. Skeletal fragility in diabetes. Ann N Y Acad Sci. 2017;1402:18-30.
3. Bonds DE, Larson JC, Schwartz AV, et al. Risk of fracture in women with type 2 diabetes: the women's health initiative observational study. J Clin Endocrinol Metab. 2006;91:3404-10.
4. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol. 2007;166:495-505.
5. Leslie WD, Lix LM, Prior HJ, Derksen S, Metge C, O'Neil J. Biphasic fracture risk in diabetes: a population-based study. Bone. 2007;40:1595-601.
6. Schwartz AV, Vittinghoff E, Bauer DC, et al. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. JAMA. 2011;305:2184-92.

7. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes-a meta-analysis. Osteoporos Int. 2007;18:427-44.
8. Yamaguchi T, Kanazawa I, Yamamoto M, et al. Associations between components of the metabolic syndrome versus bone mineral density and vertebral fractures in patients with type 2 diabetes. Bone. 2009;45:174-9.
9. Petit MA, Paudel ML, Taylor BC, et al. Bone mass and strength in older men with type 2 diabetes: the osteoporotic fractures in men study. J Bone Miner Res. 2010;25:285-91.
10. Giangregorio LM, Leslie WD, Lix LM, et al. FRAX underestimates fracture risk in patients with diabetes. J Bone Miner Res. 2012;27:301-8.
11. Leslie WD, Morin SN, Lix LM, Majumdar SR. Does diabetes modify the effect of FRAX risk factors for predicting major osteoporotic and hip fracture? Osteoporos Int. 2014;25:2817-24.
12. Lin CC, Lai MS, Syu CY, Chang SC, Tseng FY. Accuracy of diabetes diagnosis in health insurance claims data in Taiwan. J Formos Med Assoc. 2005;104:157-63.
13. Young BA, Lin E, Von Korff M, et al. Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. Am J Manag Care. 2008;14:15-23.
14. Ma L, Oei L, Jiang L, et al. Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. Eur J Epidemiol. 2012;27:319-32.
15. Oei L, Zillikens MC, Dehghan A, et al. High bone mineral density and fracture risk in type 2 diabetes as skeletal complications of inadequate glucose control: the Rotterdam Study. Diabetes Care. 2013;36:1619-28.
16. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ. 2009;180:32-9.
17. Schwartz AV, Vittinghoff E, Bauer DC, et al. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. JAMA. 2011;305:2184-92.
18. Maurer MS, Burcham J, Cheng H. Diabetes mellitus is associated with an increased risk of falls in elderly residents of a long-term care facility. J Gerontol A Biol Sci Med Sci. 2005;60:1157-62.
19. Schwartz AV, Vittinghoff E, Sellmeyer DE, et al. Diabetes-related complications, glycemic control, and falls in older adults. Diabetes Care. 2008;31:391-6.
20. Schwartz AV, Sellmeyer DE, Ensrud KE, et al. Older women with diabetes have an increased risk of fracture: a prospective study. J Clin Endocrinol Metab. 2001;86:32-8.
21. Schwartz AV. Diabetes, TZDs, and bone: a review of the clinical evidence. PPAR Res. 2006;2006:24502.
22. Leslie WD, Aubry-Rozier B, Lamy O, Hans D, Manitoba Bone Density Program. TBS (trabecular bone score) and diabetes-related fracture risk. J Clin Endocrinol Metab. 2013;98:602-9.
23. Melton LJ, Riggs BL, Leibson CL, et al. A bone structural basis for fracture risk in diabetes. J Clin Endocrinol Metab. 2008;93:4804-9.
24. Schwartz AV, Garnero P, Hillier TA, et al. Pentosidine and increased fracture risk in older adults with type 2 diabetes. J Clin Endocrinol Metab. 2009;94:2380-6.
25. Tang SY, Allen MR, Phipps R, Burr DB, Vashishth D. Changes in non-enzymatic glycation and its association with altered mechanical properties following 1-year treatment with risedronate or alendronate. Osteoporos Int. 2009;20:887-94.
26. Tseng TH, Mu CF, Hsu CY. The correlation between renal function and bone mineral density. Minerva Urol Nefrol. 2014;66:153-6.
27. Capla JM, Grogan RH, Callaghan MJ, et al. Diabetes impairs endothelial progenitor cell-mediated blood vessel formation in response to hypoxia. Plast Reconstr Surg. 2007;119:59-70.
28. Oikawa A, Siragusa M, Quaini F, et al. Diabetes mellitus induces bone marrow microangiopathy. Arterioscler Thromb Vasc Biol. 2010;30:498-508.
29. Chang HY, Weiner JP, Richards TM, Bleich SN, Segal JB. Predicting costs with diabetes complications severity index in claims data. Am J Manag Care. 2012;18:213-9.
30. Loiu JY, Mu CF, Hsu CY. Medical appointment no-shows associated with poor glycaemic control among Taiwanese aborigines. Aust J Rural Health 2012;20: 312-7.
31. Centers for Disease Control and Prevention. 2014 National Diabetes Statistics Report. https://www.cdc.gov/diabetes/data/statistics/2014statisticsreport.html
32. Ivers RQ, Cumming RG, Mitchell P, Peduto AJ. Diabetes and risk of fracture: The blue mountains eye study. Diabetes Care. 2001;24:1198-203.
33. Zoungas S, Chalmers J, Ninomiya T, et al. Association of Hb_{A1c} levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. Diabetologia. 2012;55:636-43.
34. Ceriello A, Ihnat MA, Thorpe JE. Clinical review 2: The 'metabolic memory': is more than just tight glucose control necessary to prevent diabetic complications? J Clin Endocrinol Metab. 2009;94:410-5.
35. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:129-39.
36. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545-59.
37. Viegas M, Costa C, Lopes A, Griz L, Medeiro MA, Bandeira F. Prevalence of osteoporosis and vertebral fractures in postmenopausal women with type 2 diabetes mellitus and their relationship with duration of the disease and chronic complications. J Diabetes Complications. 2011;25:216-21.

ORIGINAL ARTICLE

Hospital standardised mortality ratio: A reliable indicator of quality of care?

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ABSTRACT

Background: This study investigates (1) whether the hospital standardised mortality ratio (HSMR) model underestimates or overestimates disease severity and (2) the completeness of the data collected by administrators to calculate HSMR in a cohort of deceased patients with the diagnosis of pneumonia.

Methods: In this retrospective cohort study Pneumonia Severity Index (PSI) and Abbreviated Mortality in Emergency Department Sepsis (abbMEDS) scores and associated mortality probabilities were obtained from 32 deceased pneumonia patients over the year 2014 in the VU University Medical Centre. These were compared with mortality probabilities of the Central Bureau for Statistics (CBS) calculated for every patient using the HSMR model. Clinical charts were examined to extract relevant comorbidities to determine the reliability of data sent to the national registration of hospital care.

Results: Risk categories determined by using the PSI and the abbMEDS were significantly higher compared with the risk categories according to HSMR (p = 0.001, respectively p = 0.000). The mean difference between the number of comorbidities in our registration and the coders' registration was 1.97 (p = 0.00). The mean difference was 0.97 (p = 0.000) for the number of comorbidities of influence on the Charlson Comorbidity Index (CCI) and 1.25 (p = 0.001) for the calculated CCI.

Conclusion: The results of this study suggest that the mortality probabilities as calculated by the CBS are an underestimation of the risk of dying for each patient. Our study also showed that the registration of data sent to the CBS underestimated the actual comorbidities of the patient, and could possibly influence the HSMR.

KEYWORDS

Data registration, disease severity, HSMR, patient outcomes, quality indicator

INTRODUCTION

Since March 2014, Dutch hospitals are obliged to be transparent about their mortality rates.[1] To be able to compare the quality of hospital care using their mortality rate, these rates have to be standardised in order to correct for the differences in the case-mix.[2] This standardised ratio is represented in the hospital standardised mortality ratio (HSMR) and is the ratio of the observed to the expected deaths, derived from data from the national registration of hospital care, the LBZ.[3] The expected deaths are calculated with the use of a statistical model that corrects for certain factors such as age, socioeconomic status and comorbidity.[3] In 2014, this model contained standardised mortality ratios (SMRs) for 50 diagnosis groups, which account for 80% of in-hospital deaths. This was extended to SMRs for 157 diagnosis groups in 2015.

Over the year 2014, the VU Medical Centre, Amsterdam (VUmc) had a relatively high HSMR, in part caused by a high SMR for the diagnosis group 'pneumonia'. The SMR of a diagnosis group can be used to investigate the cause of unexpected high mortality in a hospital more specifically than by solely using the HSMR.[4] For this reason a commission of independent external investigators in the VUmc were asked to investigate this high SMR. The aim was to investigate whether preventable/avoidable factors contributed to these deaths. Their report showed no avoidable causes of death in this cohort. These findings

suggest that the cause of the high SMR for pneumonia is probably due to other unknown factors. It could, for example, be caused by insufficient registration of comorbidities or wide variations in disease severity. In the clinical setting, physicians and nurses use several different scoring systems to determine the severity and to predict the mortality of pneumonia using patient characteristics such as age, blood urea and respiratory rate. Two of the best-validated and most used scoring systems are the Pneumonia Severity Index (PSI)[5] and the Abbreviated Mortality in Emergency Department Sepsis score (abbMEDS).[6]

The HSMR is calculated by the Central Bureau of Statistics (CBS) and the data used for this calculation are registered by Dutch Hospital Data (DHD) within the context of the LBZ. The Medical Administration Office of each hospital provides the information that is used. The HSMR is, among other covariates, derived from the primary diagnosis and the Charlson Comorbidity Index (CCI),[7] which are obtained from patients' charts and documented by coders. This underlines the importance of a complete administration, as deficient or faulty data might directly influence the HSMR. Van der Laan et al. (2013)[8] showed that the effect of registering 10% more comorbidities could result in a decrease of 5 points of the HSMR.[8] Although the administration of data has improved significantly since the implementation of the HSMR as an indicator of quality of care, there still might be inconsistencies in the comorbidity data extracted by coders and registered by DHD, when compared with the actual data extracted by doctors from the patients' charts.[8,9]

Therefore, the main aim of this study was to examine whether the HSMR model underestimates or overestimates the disease severity of pneumonia patients when compared with routinely used clinical severity scores. Our secondary aim was to investigate the completeness of the data sent to DHD to calculate the HSMR.

MATERIAL AND METHODS

In 2014, 32 deceased patients were registered in the 'pneumonia' group at the VUmc. In order to obtain PSI and abbMEDS scores for these patients, patients' charts were examined for information needed to calculate these scores from which corresponding mortality probabilities could be calculated. Missing information was considered as not contributing to the score.

The HSMR is calculated by logistic regression using the below-mentioned covariates with data provided by hospital coders. With this information, regression coefficients for these covariates are estimated and are used to calculate mortality probabilities for each individual admission.[3] The results of the calculations are send to each hospital in the annual HSMR report.

The HSMR is calculated using the following covariates[3]:

- Age at admission
- Sex
- Socioeconomic status (SES) of the postal area of the patient's address. The SES classification per postal code is compiled by the Netherlands Institute for Social Research (SCP)
- Severity of main diagnosis. Instead of CCS diagnosis subgroups (Clinical Classifications Software: a tool to cluster patient diagnoses into a manageable number of clinically meaningful categories, based on the International Classification of Diseases. The CCS makes little distinction in regard to disease severity when categorising diagnosis codes), a classification of severity of the main diagnosis in terms of mortality rates is used, as suggested by Van den Bosch et al. (2011)[10]
- Urgency of admission (elective, acute)
- Comorbidity (17 comorbidity groups of the Charlson Comorbidity Index[7])
- Source of admission (home, nursing home or other institution, hospital)
- Year of discharge
- Month of admission

In order to compare the mortality probabilities derived from the PSI and abbMEDS scores (which correspond with ordinal risk categories) and the mortality probabilities calculated by the CBS (which can be considered a continuous variable), new categories needed to be formed for the latter. It was decided to form three sets of categories from the CBS data, one for each of the scores. *Table 1* shows the risk categories and corresponding mortality probabilities of the three scoring systems. The consensus was that the best way to establish limits for new categories was by using the median between each of the mortality probabilities, as those are the means of that risk category. As can be seen in *table 1*, the lowest risk categories of the PSI predict a risk of 0.1% and of 0.6%. The median between these risks is 0.35, therefore, the limits of the

Table 1. *Risk categories and corresponding mortality probabilities of the scoring systems*

PSI[5]		abbMEDS[6,13]	
Low risk I	0.1%	Low risk	3.6%
Low risk II	0.6%	Intermediate risk	19.5%
Low risk III	0.9%	High risk	46.2%
Medium risk	9.5%		
High risk	26.7%		

The mortality probabilities of the risk categories for the abbMEDS score are derived from a study by Roest et al. (2015)[13]

PSI categories used are 0-0.35; 0.35-0.75; 0.75-5.2; 5.2-18.1; 18.1-100 and the limits for the abbMEDS are 0-11.55; 11.55-32.85; 32.85-100.

The newly formed categories of the CBS calculated mortality probabilities were compared with the categories of the PSI and abbMEDS scores. A Wilcoxon sign-rank test was used for statistical analysis to test for conformity.

To investigate whether data sent to DHD significantly differed from what is found in patients' charts, data were gathered on the total amount of comorbidities that were present in charts, which of these were directly of influence to the CCI (excluding the comorbidities that are not in the Charlson Comorbidity Index) and finally the estimated CCI by the hospital itself. The coders in VUmc primarily look at the discharge letter and only broaden their scope when they presume this to be insufficient. In this study one researcher (JVE) thoroughly checked every patient's chart which included the discharge letter. If there was any uncertainty concerning a possible comorbidity or diagnosis, a second researcher (PN) was consulted and consensus was reached. The data that the CBS used were obtained from the Medical Administration Office. A paired t-test was used to analyse the difference between our registration and the coders' registration. For all analyses, a two-tailed p-value of less than 0.05 was considered statistically significant.

RESULTS

Table 2 gives an overview of the patient characteristics of our population. Ten patients had a cause of death other than respiratory failure or sepsis.

Mortality probabilities

Table 3 illustrates the dispersion of mortality probabilities calculated by the CBS using the HSMR model and those of the two clinical scoring systems. It can be seen that for the majority of patients the estimated risk of dying within 28-30 days is much higher according to the clinical scoring systems than the estimated risk of dying as calculated using the SMR model. Especially the abbMEDS assesses the risk to be significantly higher than the CBS does. In our cohort of patients, the abbMEDS seemed to estimate the severity of pneumonia the best. This is why we categorised the table according to the risk categories of the abbMEDS.

Descriptive statistics of conformity were performed and this showed that for the PSI 18 patients were in a higher risk category than according to the CBS (SMR), 3 were in a lower category and 11 were in the same category. When looking at the abbMEDS, all patients were either in the same risk category (10) or in a higher risk category (22) compared with SMR.

Further analysis showed a significant increase in assigned risk categories for the PSI ($p < 0.001$) and for the abbMEDS ($p < 0.001$) compared with the SMR. This indicates that risks of dying of these patients, according to clinical scoring systems, were significantly higher than the risks of dying according to SMR calculated by the CBS.

Registration of data

Figure 1 shows the number of comorbidities, the number of comorbidities influencing the CCI and the calculated CCI itself from our own registration and those same outcome measures which medical coders registered. For each of the outcome measures the mean of our registered number is higher than the mean of what the coders registered.

As *table 4* shows, the mean difference between the number of comorbidities in our registration and the coders' registration is 1.97. The mean difference between our

Table 2. *Demographic and clinical characteristics of the deceased patients in the 'pneumonia' group over the year 2014*

Characteristics	Deceased patients (n = 32)	
	Number	Percentage
Demographic factor		
Age > 65 years	25	78.13
Female sex	12	37.5
Nursing home resident	6	18.75
Admissions		
≥ 2 in last 12 months	16	50
ICU admissions in last 12 months	14	43.75
Unexpectedly long admission*	6	18.75
Cause of death		
Respiratory failure	14	43.75
Sepsis	12	37.5
Myocardial infarction	5	15.63
Heart failure	4	12.5
Other	1	3.13
Other clinical characteristics		
Immunocompromised§	10	31.25
Do not resuscitate	26	81.25
Polypharmacy±	28	87.5
Limited mobility&	24	75
Delirium	8	25
Malnutrition$	12	37.5

Cause of death: In some patients the respiratory failure or heart failure was a direct result of sepsis.
* An admission minimally 50% longer than expected for a specific primary diagnosis. The calculation of the expected length of admission takes into account the age of the patient, primary diagnosis and any possible interventions.
§ Immunodeficiency by the use of immunosuppressive drugs, by neutropenia or leukopenia or other causes.
± The chronic use of ≥ 5 medications.
& Patient uses devices for mobility or was bedridden.
$ Patient has a Short Nutritional Assessment Questionnaire (SNAQ) score of ≥ 2 or when the patient was described as cachexic.

Table 3. *Mortality probabilities calculated by the CBS and those derived from the scoring systems, categorised according to the risk categories of the abbMEDS*

Risk category abbMEDS	Patient no.	abbMEDS	PSI	Mortality probabilities CBS (SMR)
Low risk	1	3.60%	0.60%	0.87%
	11	3.60%	9.50%	8.76%
	28	3.60%	26.70%	2.89%
Intermediate risk	2	19.50%	26.70%	6.29%
	5	19.50%	9.50%	10.01%
	6	19.50%	26.70%	3.64%
	7	19.50%	26.70%	18.02%
	9	19.50%	9.50%	10.62%
	10	19.50%	26.70%	12.19%
	13	19.50%	9.50%	18.60%
	14	19.50%	0.90%	3.45%
	16	19.50%	26.70%	5.76%
	17	19.50%	26.70%	11.02%
	19	19.50%	26.70%	6.68%
	20	19.50%	9.50%	7.74%
	21	19.50%	9.50%	5.92%
	22	19.50%	9.50%	6.18%
	23	19.50%	26.70%	24.59%
	24	19.50%	26.70%	10.54%
	25	19.50%	9.50%	13.70%
	26	19.50%	9.50%	5.01%
	27	19.50%	9.50%	1.54%
	30	19.50%	9.50%	12.87%
	32	19.50%	9.50%	21.24%
High risk	3	46.20%	26.70%	14.70%
	4	46.20%	9.50%	6.43%
	8	46.20%	26.70%	15.33%
	12	46.20%	26.70%	18.05%
	15	46.20%	26.70%	5.39%
	18	46.20%	26.70%	9.34%
	29	46.20%	26.70%	6.32%
	31	46.20%	26.70%	13.37%

Green represents higher probability than calculated by the CBS (using the SMR-model), red represents a lower probability.

registration and the coders' registration for the CCI is 1.25. All of these results are statistically significant.

An unanticipated finding was that the source of admission was 'home' in every case. It seemed as though no distinction was made between 'home' and 'nursing home'. Nevertheless, *table 1* shows that 6 out of 32 patients were admitted from a nursing home.

DISCUSSION

The findings in this paper indicate that (1) the SMR model appears to underscore the severity of pneumonia compared with the validated clinical scoring systems PSI and abbMEDS in a cohort of patients who died of pneumonia; and (2) the total number of comorbidities and the number of comorbidities influencing the CCI is higher according to our registration than according to the coders' registration.

The results in this study further support the suggestion that was made by Pleizier et al. that the SMR for more diagnosis groups besides cerebrovascular diseases will also decrease when adjusted for the severity of disease.[11] They concluded that within the SMR group 'cerebrovascular diseases' there is no distinction between 'stroke', 'cerebral haemorrhage' and 'subarachnoid haemorrhage' while their mortality rates differ greatly.[11] The mortality rates were 18, 43 and 35%, respectively, and when these differences were not taken into account, the influence on the SMR

Figure 1. *Compared means and SD of the outcome measures extracted during our study versus what coders registered and the CBS used to calculate the HSMR*

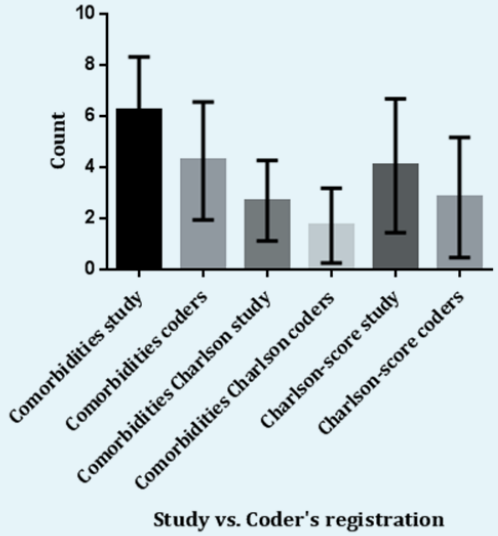

Table 4. *Statistical analysis of the outcome measures*

	Mean	SD	SE	95% CI	p-value
Comorbidities study – comorbidities CBS	1.96875	2.53345	.44785	1.05535-2.88215	.000
Charlson Index Study – Charlson index CBS	1.25000	1.95101	.34489	.54658-1.95342	.001

Outcome measures in the table are the number of comorbidities and the Charlson Comorbidity index. SD = standard deviation; SE = standard error of the mean.

could be considerable.[12] They recalculated the SMR for 'cerebrovascular diseases' after correcting for the above-mentioned sub-diagnoses and found that this gave a reduction from 119 (95% CI 105-133) to 102 (95% CI 91-115).[11] Beside this diagnosis group, this is possibly also true for other SMR groups such as the 'pneumonia group'. A subdivision for 'cerebrovascular diseases' was easily made by just looking at the mortality rates for several subdiagnoses within that group. This, however, is a lot harder for a diagnosis group such as 'pneumonia', where there are no known distinct subdiagnoses. To make a subdivision for 'pneumonia', two different scoring systems were used that indicate severity of disease. The best way to prove that a subdivision by each of these scores has a direct effect on the SMR is by adjusting the SMR model in the same way Pleizier et al. did.[11] They incorporated a division in risk categories into the logistic regression model, just as the other covariates. In our study, it was decided to compare the mortality probabilities of the validated scores with the mortality probabilities calculated by the CBS with the use of the SMR model.

The results show that for the large majority of patients the expected mortality within 28-30 days is much higher according to the two scoring systems than to the score calculated by the CBS. This is probably partly caused by underscoring the number of comorbidities, but also a lack of proper adjustment for the severity of the disease pneumonia in the individual patient. These two scoring systems are widely used in clinical settings when dealing with pneumonia patients and have been validated.[5,13] They are specifically designed to assess the severity of pneumonia/sepsis and should therefore be taken seriously as predictors of death. This suggests that the mortality probabilities according to the HSMR model of CBS are an underestimation of the real risk of dying for each patient. Naturally, estimating disease severity with the use of nine variables results in a simplification of reality. In addition, it is known that university medical centres predominantly provide tertiary care for a case-mix of patients with a higher severity of disease than peripheral hospitals. Therefore, they might falsely have a 'higher' HSMR.

Our results indicate that the mortality probabilities calculated by the PSI and the abbMEDS are higher than what the CBS calculated. It could be argued that the steps between the risk categories of these scoring systems are fairly big. Therefore, when a patient is placed in the highest risk category of, for example, the abbMEDS their risk of dying could be even higher than 46.2%. However, *table 3* does compare categorical variables (the mortality probabilities calculated by the scoring systems) with a continuous variable (the mortality probabilities calculated by the CBS), which implies that these risks will almost always differ from the risks as calculated by the CBS.

The secondary aim of this study was to assess the registration of comorbidities from the patients' charts by medical coders. As stated earlier, we discovered that the source of admission was 'home' in every case, although six of the patients in our cohort were admitted from a nursing home. This could potentially have an impact on the HSMR as a whole; however, this influence is probably rather small. It must be acknowledged that the source of admission is not primarily registered by coders, but they are responsible for checking this registration.

Van der Laan et al. already underlined the influence of the registered number of comorbidities on the HSMR.[8] With this in mind, an average difference of two registered comorbidities seems significant enough to be of influence to the HSMR. For a comorbidity to be of influence to the HSMR it needs to add to the CCI; so, to make the previous assumption more likely, the CCI of every patient was also taken in consideration. It was found that there was a statistically significant difference of 1.25 points between the calculated CCI based on our registration and the calculated CCI based on the coders' registration. This strongly suggests that the apparently insufficiently registered number of comorbidities does directly influence the HSMR. As stated earlier, coders are dependent on proper documentation by others, including doctors. They primarily look at the discharge letter and operation reports, and are not expected to go through the entire patient chart, mainly since this would be too time consuming. This lack of time might be one of the causes of the apparent under registration of comorbidities. One other cause explaining the under registration is that according to coding protocol, sometimes an International Classification of Diseases (ICD-10) code which has less impact on the HSMR than the actual diagnosis has to be selected. Although the precise impact cannot be judged by the results of this study, these findings do raise the question whether the

HSMR is reliable enough to estimate what it is supposed to do or to be published for everyone to see.

The limitations of this work must be acknowledged. The self-formed categories composed to compare categorical and continuous variables are merely based on what was thought to be the most logical way to do this. Hence, a note of caution is due here when interpreting these results. Also, in this study no control group was investigated. This withholds the opportunity to compare the mortality probabilities of the living patients with the deceased patients and therefore we were not able to investigate if the severity of disease was greater in the deceased group. Finally, it would have been interesting to calculate the HSMR/SMR using our calculated CCI and compare this with the HSMR/SMR calculated by the CBS. Unfortunately, computing our own logistic regression model to perform these calculations proved to be too time consuming.

CONCLUSION

Hospitals are obliged to publish their HSMRs, which gives patients and healthcare institutions the opportunity to judge and compare hospitals on the basis of this number. However, we demonstrated that differences in case-mix and the incompleteness of the data used to calculate the HSMR could negatively influence the HSMR. Although it seems quite logical to look at the number of deaths in each hospital as an indicator of quality of care, there are numerous pitfalls hidden in using the HSMR as a quality indicator. Therefore, HSMR should always be interpreted with caution and openly publishing HSMRs may have unfair negative consequences for some hospitals.

DISCLOSURES

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REFERENCES

1. Hospital Standardised Mortality Ratio, de Praktijk Index, www.hsmr.nl. Accessed January 2017.
2. Understanding HSMRs. A Toolkit on Hospital Standised Mortality Ratios. http://www.drfoster.com/wp-content/uploads/2014/09/HSMR_Toolkit_Version_9_July_2014.pdf. Published 2014. Accessed December 2016.
3. Van der Laan J, de Bruin A, van den Akker-Ploemacher J, Penning C, Pijpers F. HSMR 2014 methodological report, november 2015. http://www.hsmr.nl/wp-content/uploads/2016/01/2015hsmrmethodologicalreport2014.pdf. Accessed November, 2016.
4. Jarman B, Pieter D, van der Veen AA, et al. The hospital standardised mortality ratio: a powerful tool for Dutch hospitals to assess their quality of care? Qual Saf Health Care. 2010;19:9-13.
5. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336:243-50.
6. Vorwerk C, Loryman B, Coats TJ, et al. Prediction of mortality in adult emergency department patients with sepsis. Emerg Med J. 2009;26:254-8.
7. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-83.
8. Central bureau of statistics (Van der Laan J). Quality of the Dutch Medical Registration (LMR) for the calculation of the Hospital Standardised Mortality Ratio. 2013; ISSN: 1572-0314.
9. Tol J, Broekman M, Brauers M, van Gulik T, Busch OR, Gouma DJ. [Reliability of the registration of data on complex patients: effects on the hospital standardised mortality ratio (HSMR) in the Netherlands]. Ned Tijdschr Geneeskd. 2012;156:A4918.
10. Van den Bosch WF, Spreeuwenberg P, Wagner C. [Hospital standardised mortality ratio (HSMR): adjustment for severity of primary diagnosis can be improved]. Ned Tijdschr Geneeskd. 2011;155:A3299.
11. Pleizier CM, Geerlings W, Pieter D, Boiten J. Patientmix influences HSMR. Medisch Contact 2010. 36:1777-9.
12. Bots ML, Jager-Geurts H, Berger-van Sijl M. Risk of dying after first hospita ladmission for a cerebrovascular accident in the Netherlands. Cardiovascular disease in the Netherlands. The Hague, 2006.
13. Roest AA, Tegtmeier J, Heyligen JJ, et al. Risk stratification by abbMEDS and CURB-65 in relation to treatment and clinical disposition of the septic patient at the emergency department: a cohort study. BMC Emerg Med. 2015;15:29.

ORIGINAL ARTICLE

Residents' readiness for out-of-hours service: a Dutch national survey

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ABSTRACT

Background: Residents play a crucial role in out-of-hours service. Their perceived readiness for out-of-hours service, however, remains underexposed. This national exploratory study assesses whether or not Dutch residents feel sufficiently prepared to provide out-of-hours service at the time of their first shift, and aims to identify factors influencing perceived readiness.

Methods: An online questionnaire focussing on residents' working conditions was accessible from 21 September to 10 November 2015. Questions targeting perceived readiness for out-of-hours service were presented to all responding medical residents actively involved in out-of-hours service. Residents who felt sufficiently prepared were compared with residents who did not, exploring both individual characteristics and environmental factors.

Results: A total of 960 residents (mean age 32.5 years ± 3.5, 72.4% female) from over 30 different medical specialties were included. Thirty-six percent of responding residents felt insufficiently prepared to provide out-of-hours service at the time of their first shift. Current junior status ($p = 0.020$), prolonged clinical experience prior to the first shift ($p < 0.001$), targeted training ($p < 0.001$), assessment of relevant skills and competencies ($p < 0.001$), and formal consequences following negative assessment ($p = 0.001$) were positively associated with perceived readiness.

Conclusion: One-third of responding residents felt insufficiently prepared for their first out-of-hours shift. Our results emphasise the need for sufficient time to gain clinical experience as a new graduate, and underline the positive contribution of targeted training and assessment of skills and competencies relevant to out-of-hours service.

KEYWORDS

Acute care, out-of-hours service, readiness for practice, resident

INTRODUCTION

The importance of timely identification and adequate resuscitation of critically ill patients, as a means to save lives and reduce the number of intensive care admissions, has long been established.[1] Residents play a crucial role in this primary assessment, as they are often the first to see the patient.[2,3] This is certainly the case during out-of-hours service, when bedside supervision is often not immediately available. Concerns have been raised about potential negative effects of this practice on patient safety. Especially junior residents, having limited clinical experience, may well lack the skills and competencies required to deliver out-of-hours service, and acute care in particular, at a high standard.[4-7]

Several studies have been published discussing the general transition from medical school to clinical practice.[8-10] Residents' perceived readiness specifically for out-of-hours service, however, remains underexposed. Previous research demonstrates the challenges junior residents face in this context and emphasises that providing a high standard of care to critically ill patients requires more than knowledge and skills.[11-13]

The Dutch medical curriculum[14] shows much resemblance to other medical curricula.[15] A three-year bachelor program consisting of mainly problem-based education is followed by a three-year master program incorporating clinical clerkships in a variety of hospital departments and general practice. Generally, clerks will experience increasing levels of responsibility during their training. After finishing their undergraduate education, most graduates will start a residency training program and work under supervision for 3-6 years before practising medicine independently. Traditionally, residents will start participating in out-of-hours service within their first months of clinical practice.

The primary goal of this national exploratory study was to assess whether or not Dutch residents feel sufficiently

prepared to provide out-of-hours service at the time of their first shift. Secondly, we aimed to identify factors influencing perceived readiness.

MATERIALS AND METHODS

This national exploratory study targeted Dutch residents of all levels of experience and different medical specialties, actively involved in out-of-hours service. Residents not involved in out-of-hours service, or not participating in the acute care setting whilst providing out-of-hours service, were excluded. Residents still within their first year of specialty training were labelled junior residents, residents in higher years of specialty training were labelled senior residents.

Data collection

In collaboration with the Dutch Federation of Young Medical Specialists, a link to an online questionnaire was made available from 21 September to 10 November 2015. All active federation members (n = 2626, September 2015) received an email inviting them to participate. Also, the questionnaire could be accessed by non-members through the Dutch Federation of Young Medical Specialists website, which was repeatedly announced on social media and in national medical journals.

Questionnaire

The questionnaire contained a total of 194 questions (a combination of previously validated questionnaires and newly composed questions), focussing on residents' working conditions. Fourteen newly composed questions were relevant to this study (*table 1*). Question formats were multiple choice, numerical response, yes or no, or free text. Ethical approval for this study was obtained from the Dutch Society for Medical Education Ethical Review Board (file number: 342).

Data analysis

Current medical specialty was categorised into *surgical*, *non-surgical*, *supporting* and *other specialties*. The total number of months of clinical experience prior to the first out-of-hours shift was categorised into 0 to < 3 months, 3 to < 6 months, 6 to < 9 months, 9 to < 12 months and > 12 months, which corresponds to the quarterly assessment of junior residents, as is common in most first year residency training programs. Using SPSS 22 descriptive statistics, overall baseline characteristics were collected. Residents who felt sufficiently prepared were compared with residents who did not, exploring both individual characteristics and environmental factors. Chi square tests and independent samples T-tests were performed as appropriate. A p-value < 0.05 was considered statistically significant.

Table 1. *Questions regarding baseline characteristics and residents' readiness for out-of-hours service*

1.	What is your year of birth?
2.	What is your gender?
3.	In what year did you graduate from medical school?
4.	Where are you currently employed?
5.	Which university medical centre is your hospital affiliated with?
6.	What is your current training specialty?
7.	What is your current year of specialty training?
8.	Do you participate in out-of-hours service?
9.	'As part of the out-of-hours service I provide, I work in the emergency department and/or care for critically ill patients.'
10.	At the time of your first shift, did you feel sufficiently prepared to provide out-of-hours service?
11.	How many months of clinical experience had you gained as a medical resident, at the time of your first out-of-hours shift?
12.	Did you attend a course targeting out-of-hours service prior to your first out-of-hours shift?
13.	Were basic skills and competencies assessed prior to your first out-of-hours shift?
14.	Were measures taken when residents failed to meet the requirements for providing out-of-hours service?

RESULTS

A total of 1220 residents from over 30 different medical specialties responded. After excluding residents who were not involved in out-of-hours service (n = 81) or who did not actively participate in the acute care setting whilst providing out-of-hours service (n = 179), a total of 960 residents remained for final analysis (*figure 1*).

Baseline characteristics

The 960 residents had a mean age of 32.5 years (SD ± 3.5); 695 residents were female (72.4%, *table 2*). On average, residents had completed their undergraduate medical education 6.7 years earlier (SD ± 3.0). Residents had chosen a surgical specialty in 28.5%, a non-surgical specialty in 57.6%, and a supporting specialty in 9.1%. The remaining 4.8% selected 'other'. Eighteen percent of responding residents were labelled junior residents. Overall, 42.6% currently worked in a university medical centre, 47.3% in a district general hospital, and 10.1% worked elsewhere.

Residents' readiness for out-of-hours service

Of the residents, 614 (64.0%) felt sufficiently prepared for their first out-of-hours shift, 346 residents (36.0%)

Figure 1. *Respondents available for final analysis*

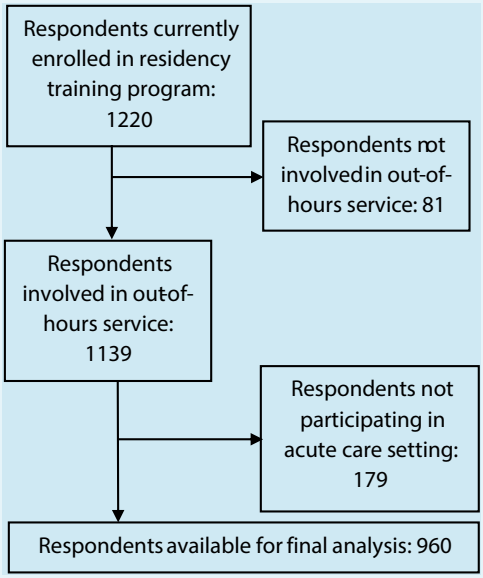

Table 2. *Baseline characteristics (n = 960)*[a]

Age (mean ± SD)	32.5 ± 3.5
Gender	
Female	695 (72.4%)
Male	265 (27.6%)
Number of years since graduation (mean ± SD)	6.7 ± 3.0
Current specialty[b]	
Surgical	274 (28.5%)
Non-surgical	553 (57.6%)
Supporting	87 (9.1%)
Other	46 (4.8%)
Current year of specialty training (mean ± SD)	3.1 ± 1.5
Junior versus senior[c]	
Junior	173 (18.0%)
Senior	787 (82.0%)
Current site of employment	
University Medical Centre	409 (42.6%)
District General Hospital	454 (47.3%)
Other[d]	97 (10.1%)

[a] Data are represented as number of respondents (percentage) unless otherwise indicated.
[b] Respondents chose their current specialty from a list of acknowledged medical specialties. Responses were subsequently categorised. Surgical: cardiothoracic surgery, general surgery, ear nose and throat surgery, neurosurgery, ophthalmology, orthopaedics, plastic surgery, urology, gynaecology/obstetrics. Non-surgical: cardiology, dermatology, internal medicine, paediatrics, geriatrics, pulmonology, gastroenterology, neurology, psychiatry, rheumatology, rehabilitation medicine, emergency medicine, general hospital medicine. Supporting: anaesthesiology, clinical chemistry, clinical physics, clinical genetics, medical microbiology, nuclear medicine, pathology, radiology, radiotherapy, hospital pharmacy. Other: all remaining, not previously specified specialties.
[c] Residents within first year of specialty training: junior residents. Residents in higher years of specialty training: senior residents.
[d] E.g. rehabilitation centre, mental health institute.

did not (*table 3*). The two groups were subsequently compared, exploring both individual characteristics and environmental factors. The difference in mean age (32.3 and 32.8 years, respectively), although statistically significant (p = 0.030), was minimal. No influence of gender (p = 0.328) or chosen medical specialty (p = 0.139) was observed. The percentage of junior residents was significantly higher amongst residents who felt sufficiently prepared (20.2%) compared with residents who did not (14.2%, p = 0.020). A total of 631 residents (65.7%) were enrolled in out-of-hours service within their first three months of clinical practice. Prolonged clinical experience prior to the first out-of-hours shift, however, was associated with an increased sense of readiness (p < 0.001). Furthermore, the percentage of residents who had received additional training targeting out-of-hours service was higher amongst residents who felt sufficiently prepared (46.3%) compared with residents who did not (30.3%). Attending targeted training was associated with a significant increase in perceived readiness (p < 0.001). The majority of residents who felt sufficiently prepared had undergone some form of assessment of relevant skills and competencies prior to their first shift (70.7%). This percentage was lower amongst residents who felt insufficiently prepared (52.3%). Overall, assessment was associated with an increased sense of readiness (p < 0.001). Finally, formal consequences following negative assessment also showed a positive association with perceived readiness (p = 0.001).

DISCUSSION

This study reviewed residents' readiness for out-of-hours service as perceived by 960 Dutch medical residents. While 64% of residents felt sufficiently prepared for their first out-of-hours shift, a disturbing 36% did not. This lack of perceived readiness in acute care amongst junior residents was also noted by Tallentire et al. in a systemic literature review following the implementation of Tomorrow's Doctors in the United Kingdom.[16,17] Although hardly an ideal surrogate for actual preparedness, perceived preparedness in acute care is known to impact junior residents' behaviour and therefore warrants further consideration.[11] We found several factors possibly attributing to the primary outcome in our study population.

The percentage of junior residents was higher amongst residents who felt sufficiently prepared compared with residents who did not. Recent revision of the Dutch medical curriculum could partially explain this observation, similar to how the introduction of *Tomorrow's Doctors* changed perceived readiness for practice in the United Kingdom.[9,16,17] Studies evaluating the impact of

Table 3. *Residents' readiness for out-of-hours service (n = 960)*[a]

Characteristic	Sufficiently prepared (n = 614)	Insufficiently prepared (n = 346)	p-value
Age (mean ± SD)	32.3 ± 3.5	32.8 ± 3.3	***p = 0.030***
Gender			p = 0.328
Female	438 (71.3%)	257 (74.3%)	
Male	176 (28.7%)	89 (25.7%)	
Current specialty			p = 0.139
Surgical	181 (29.5%)	93 (26.9%)	
Non-surgical	340 (55.4%)	213 (61.6%)	
Supporting	64 (10.4%)	23 (6.6%)	
Other	29 (4.7%)	17 (4.9%)	
Current year of specialty training (mean ± SD)	3.0 ± 1.5	3.4 ± 1.5	***p = 0.001***
Junior versus senior			***p = 0.020***
Junior	124 (20.2%)	49 (14.2%)	
Senior	490 (79.8%)	297 (85.8%)	
Months of clinical experience prior to first shift[b] **(mean ± SD)**	8.1 ± 13.1	2.8 ± 4.7	***p < 0.001***
Categorisation clinical experience prior to first shift			***p < 0.001***
0 ≤ x < 3 months	357 (63.9%)	274 (86.7%)	
3 ≤ x < 6 months	53 (9.5%)	23 (7.3%)	
6 ≤ x < 9 months	11 (2.0%)	1 (0.3%)	
9 ≤ x < 12 months	30 (5.4%)	8 (2.5%)	
> 12 months	108 (19.3%)	10 (3.2%)	
Targeted training[c]			***p < 0.001***
Yes	284 (46.3%)	105 (30.3%)	
No	330 (53.7%)	241 (69.7%)	
Assessment of skills and competencies[d]			***p < 0.001***
Yes	434 (70.7%)	181 (52.3%)	
No	180 (29.3%)	165 (47.7%)	
Consequences following negative assessment[e]			***p = 0.001***
Yes	537 (87.5%)	274 (79.2%)	
No	77 (12.5%)	72 (20.8%)	

[a] Data are represented as number of respondents (percentage) unless otherwise indicated, comparing residents who felt sufficiently prepared (n = 614) to residents who did not (n=346).
[b] The large number of respondents in the '> 12 months' category amongst residents who felt sufficiently prepared is likely to explain the striking difference in mean and SD.
[c] Both nationally and internationally acknowledged courses, as well as local initiatives.
[d] E.g. written/scenario exams, clinical observation and/or completion of the Dutch Federation of Young Medical Specialists checklist (checklist addressing skills and competencies required to provide out-of-hours service).
[e] E.g. postponement of first shift, additional training, intensified supervision.

Tomorrow's Doctors suggest that recent changes in UK undergraduate training, while improving readiness in some areas, may have neglected acute care.[16] On the other hand, having gained more clinical experience, senior residents could have become increasingly aware of their shortcomings, retrospectively influencing their personal assessment.

Most residents in our study population had their first shift well within their first three months of clinical practice. From an educational perspective, however, prolonging the time to gain clinical experience before engaging in out-of-hours service was associated with an increased sense of readiness. Our results suggest a tipping point somewhere around three months. To the best of our knowledge, no consensus exists regarding the minimally required number of months of clinical experience for new graduates prior to engaging in out-of-hours service, nor has this topic been previously explored. This subject therefore deserves further attention in the future.

The attendance of courses targeting aspects of out-of-hours care, although hardly common practice in either group, was associated with a higher sense of readiness as well, in accordance with previous findings.[18,19] Unfortunately, these courses are often optional and/or not easily accessible, due to time-investment issues and costs. Also, courses vary considerably with regards to quality and content, mostly focussing on a specific subset of technical skills. The educational effects of handling the

increased responsibility and 'learning on the job' during out-of-hours service, however, could be a valid reason for continuing current practice[20,21] incorporating several, if not all, of the CanMEDS competencies[22] in one complex task. The ideal timing, content and design of a course targeting out-of-hours service, remain to be determined.

Overall, assessment of relevant skills and competencies was associated with an increased sense of readiness. The checklist for new graduates, as mentioned in *table 3*, was first developed in 2011 and addresses skills and competencies required to provide high-standard care during out-of-hours service. Formal guidelines on how to acquire these skills and competencies to a certain predetermined level, however, are lacking, and the overall familiarity with the checklist seems low.

Finally, consequences following negative assessment, of which the necessity with regards to patient safety should seem self-evident to everyone involved, were associated with an increase in perceived readiness. It is plausible that residents felt reassured, knowing they would not be enrolled in out-of-hours service if their supervising attendants did not judge them competent. This would support the need for a competency-based approach to the timing of the first out-of-hours shift, rather than the now commonly used time-based approach.

There are several limitations to our study. First of all, although all residents in training could participate, only members of the Dutch Federation of Young Medical Specialists were actively approached, possibly introducing bias. Looking at the baseline characteristics, chosen medical specialties, and current site of employment though, our study population appears to be a reliable reflection of the current distribution of medical residents in our country. This survey targeted current working conditions rather than working conditions at the time of the first out-of-hours shift. Organisational aspects of acute care, such as 24/7 coverage of the emergency department by emergency physicians, could therefore not be assessed as contributing factors. Furthermore, asking participants retrospectively about their experiences as a junior resident may introduce recall bias. The tool we used for distribution of our questionnaire and the fact that this study was part of a much larger national questionnaire targeting residents' working conditions, limited the number of questions we could present to our respondents and impacted the question formats we could use. As a result, we did not generate the level of detail needed for more in-depth analysis. Also, considering that this study was carried out within the Dutch health care system, results may not be totally applicable in other contexts. Finally, most literature focuses on acute care in particular, rather than out-of-hours service in general. Although caring for critically ill patients is a substantial part of the out-of-hours service, this made a comparison between our results and previous literature difficult.

In conclusion, 36% of responding residents felt insufficiently prepared for out-of-hours service at the time of their first shift. Our results emphasise the need for sufficient time to gain clinical experience as a new graduate, and underline the positive contribution of targeted training and assessment of skills and competencies relevant to out-of-hours service. For future research, we recommend conducting a prospective longitudinal study, following new graduates through their first year of clinical practice, with special focus on the first out-of-hours shift. Aside from identifying further challenges junior residents face in this context, this longitudinal study could also shed light on learning processes that occur during out-of-hours shifts, explore the optimal form and duration of clinical preparation for this complex task, and determine the best form of guidance during the first out-of-hours shift. Finally, considering our findings regarding training and assessment, we propose designing an educational program incorporating training and subsequent assessment of all skills and competencies relevant to out-of-hours service.

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DISCLOSURES

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REFERENCES

1. McQuillan P, Pilkington S, Allan A, et al. Confidential inquiry into quality of care before admission to intensive care. BMJ. 1998;316:1853-8.
2. Tallentire VR, Smith SE, Skinner J, Cameron HS. Exploring patterns of error in acute care using framework analysis. BMC Med Educ. 2015;15:3.
3. Van Asbroeck PJ, Heiser J, Leto R, Capizzi M, Mohrhardt C, Carenzo L. Emergency Medicine training and working conditions in Europe: a joint

EuSEM young doctors – European Junior Doctors Survey. Eur J Emerg Med. 2015;22:445-7.

4. Smith GB, Poplett N. Knowledge of aspects of acute care in trainee doctors. Postgrad Med J. 2002;78:335-8.
5. Frost PJ, Wise MP. Early management of acutely ill ward patients. BMJ. 2012;345:e5677.
6. Richardson LC, Lehnbom EC, Baysari MT, Walter SR, Day RO, Westbrook JI. A time and motion study of junior doctor work patterns on the weekend: a potential contributor to the weekend effect? Intern Med J. 2016;46:819-25.
7. Contri E, Bonomo MC, Costantini G, et al. Are final year medical students ready to save lives in Italy? Not yet. Emerg Med J. 2017;34:556. Epub 2017 Jun 21.
8. Prince K, Van de Wiel M, Van der Vleuten C, Boshuizen H, Scherpbier A. Junior doctors' opinions about the transition from medical school to clinical practice: a change of environment. Educ Health (Abingdon). 2004;17:323-31.
9. Cave J, Woolf K, Jones A, Dacre J. Easing the transition from student to doctor: how can medical schools help prepare their graduates for starting work? Med Teach. 2009;31:403-8.
10. Cameron A, Millar J, Szmidt N, Hanlon K, Cleland J. Can new doctors be prepared for practice? A review. Clin Teach. 2014;11:188-92.
11. Tallentire VR, Smith SE, Skinner J, Cameron HS. Understanding the behaviour of newly qualified doctors in acute care contexts. Med Educ. 2011;45:995-1005.
12. Mache S, Bernburg M, Baresi L, Groneberg D. Mental health promotion for junior physicians working in emergency medicine: evaluation of a pilot study. Eur J Emerg Med. 2016 Nov 22.
13. Monrouxe LV, Grundy L, Mann M, et al. How prepared are UK medical graduates for practice? A rapid review of the literature 2009-2014. BMJ Open. 2017;7:e013656.
14. Ten Cate O. Medical education in The Netherlands. Med Teach. 2007;29:752-7.
15. Wijnen-Meijer M, Burdick W, Alofs L, Burgers C, ten Cate O. Stages and transitions in medical education around the world: clarifying structures and terminology. Med Teach. 2013;35:301-7.
16. Tallentire VR, Smith SE, Skinner J, Cameron HS. The preparedness of UK graduates in acute care: a systematic literature review. Postgrad Med J. 2012;88:365-71.
17. General Medical Council. Tomorrow's Doctors – Outcomes and standards for undergraduate medical education. 2009.
18. Min AA, Stoneking LR, Grall KH, Spear-Ellinwood K. Implementation of the Introductory Clinician Development Series: an optional boot camp for Emergency Medicine interns. Adv Med Educ Pract. 2014;5:275-9.
19. Rogers GD, McConnell HW, de Rooy NJ, Ellem F, Lombard M. A randomised controlled trial of extended immersion in multi-method continuing simulation to prepare senior medical students for practice as junior doctors. BMC Med Educ. 2014;14:90.
20. Hanson JT, Pierce RG, Dhaliwal G. The new education frontier: clinical teaching at night. Acad Med. 2014;89:215-8.
21. Illing JC, Morrow GM, Rothwell nee Kergon CR, et al. Perceptions of UK medical graduates' preparedness for practice: a multi-centre qualitative study reflecting the importance of learning on the job. BMC Med Educ. 2013;13:34.
22. Frank JR (Ed). 2005. The CanMEDS 2005 Physician Competency Framework. Better standards. Better physicians. Better care. Ottawa: The Royal College of Physicians and Surgeons of Canada.

CASE REPORT

Pancreatitis as the presenting symptom of abdominal sarcoidosis

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ABSTRACT

We present a 60-year-old woman with non-pulmonary sarcoidosis manifesting as acute pancreatitis, possibly due to hypercalcaemia. Pancreatitis in sarcoidosis is rare, particularly as a presenting symptom. This case demonstrates that sarcoidosis should be included in the differential diagnosis of pancreatitis with hypercalcaemia, even without pulmonary signs of sarcoidosis.

KEYWORDS

Granulomatous disease, hypercalcemia, pancreatitis, sarcoidosis.

What was known on this topic?

Sarcoidosis is a granulomatous disorder that most commonly occurs in the lungs and lymph nodes and is usually detected through abnormalities on chest radiographs. Pancreatitis has never been reported as the first sign of extrapulmonary sarcoidosis, although pancreatic involvement is reported infrequently (1-5%) in postmortem studies and hypercalcaemia – which can indirectly cause pancreatitis – is present in 10-20% of sarcoidosis patients.

What does this add?

In patients presenting with pancreatitis and unexplained hypercalcaemia, abdominal sarcoidosis should be considered in the differential diagnostic work up, and should not be discarded in the absence of signs of pulmonary sarcoidosis.

INTRODUCTION

Sarcoidosis is a granulomatous disorder that usually occurs in the lungs (90%) and lymph nodes, although other organs can be affected. Pancreatic involvement in postmortem examinations ranges between 1 and 5%[1] and clinically apparent pancreatitis has been described sporadically in separate case reports.[2-7] To our knowledge, only four cases of sarcoidosis presenting as pancreatitis have been reported.[4-7] In all cases pulmonary sarcoidosis was also present. We report the case of a female patient without pulmonary sarcoidosis who presented with hypercalcaemia and acute pancreatitis which resulted from extensive abdominal sarcoidosis.

CASE REPORT

A 60-year-old woman with a psychiatric medical history presented to our emergency ward with a decreased level of consciousness (Glasgow Come Scale, E3M3V5), hypoxia, tachycardia and pain in the upper quadrants of the abdomen. Laboratory examination showed hypercalcaemia (3.24 mmol/l, corrected for albumin levels (32 g/l)), elevated amylase levels (1859 U/l), acute kidney injury (creatinine 393 µmol/l), increased inflammatory parameters (CRP 86 mg/l; leucocytes 19.5x10^9/l) and elevated lactate levels (2.8 mmol/l). Computed tomography (CT) of the abdomen showed signs of acute pancreatitis with extensive abdominal fluid collections and reactively enlarged lymph nodes (*figure 1A*). The patient was admitted to the ICU for intravenous fluid suppletion. We proceeded with further evaluation of the hypercalcaemia. Parathyroid hormone (PTH) and 25-OH vitamin D levels were low, while 1,25-OH vitamin D level was elevated (*table 1*). Vitamin A level was low, free T4 level and PTH-related protein (PTHrP) were normal.

Angiotensin-converting enzyme (ACE) level was normal and soluble interleukin 2 receptor (sIL-2R) was strongly elevated (*table 1*). CT thorax showed no lymphadenopathy nor pulmonary parenchymal abnormalities. Radiographic studies of the abdomen depicted an inhomogeneous spleen and liver with a thickening of the colon lining, omentum and mesentery (*figure 1B-C*). Histology of a lymph node left of the middle line of the stomach revealed a non-necrotising granulomatous inflammation with no evidence for acid-fast or other organisms (*figure 2*). Histology cultures were negative for tuberculous and non tuberculous mycobacteria. We thus diagnosed abdominal sarcoidosis, with evidence of involvement of the liver, spleen, and omental/mesenteric lymph glands.

During admission, the patient received continuous venovenous haemofiltration (CVVH) for the acute kidney injury, she was resuscitated twice – most likely due to intravascular hypovolaemia – and she developed delirium and pneumonia. Her calcium levels returned to normal after CVVH and her kidney function normalised. Amylase levels and inflammatory parameters returned to normal and she fully recovered clinically.

Therapy with prednisolone was initiated (2 weeks 30 mg/day followed by 4 weeks 20 mg/day) after discharge from the hospital. Albumin-corrected calcium levels decreased from 3.39 mmol/l to 2.62 mmol/l in the first month of treatment. The calcium levels remained stable under low-dose prednisone treatment and the sIL-2R levels decreased significantly (6804 pg/ml after 4 months of treatment).

Table 1. *Biochemical analysis of blood*

	Measured concentration (reference range)
Calcium*	3.24 mmol/l (2.15-2.55)
PTH	0.68 pmol/l (1.6-8.2)
PTHrP	< 0.3 pmol (0-0.6)
25-OH vitamin D	9 nmol/l (50-250)
1,25-OH vitamin D	103 pmol/l (48-161)
Vitamin A	0.9 umol/l (1.2-2.7)
TSH	8.5 mU/l (0.40-4.0)
Free T4	13.2 pmol/l (10.0-24.0)
ACE	43 U/l (10-51)
sIL-2R	28,600 pg/ml (0-2,500)

*Corrected for albumin levels (32 g/l).
PTH = parathyroid hormone; PTH-rP = parathyroid hormone-related protein; TSH = thyroid-stimulating hormone; ACE = angiotensin-converting enzyme; sIL-2R = soluble interleukin 2 receptor.

DISCUSSION

We report a patient who presented with acute pancreatitis due to sarcoidosis. The acute pancreatitis in our patient may have been secondary to the hypercalcaemia – by activation of trypsinogen by calcium deposition in the pancreatic duct[8] – or caused by pancreatic granulomatous infiltration leading to inflammation and obstruction of pancreatic drainage.[2] Seven cases of pancreatitis in sarcoidosis have been described previously in which all but one[3] had concomitant hypercalcaemia. About 10-20% of patients with sarcoidosis have hypercalcaemia, due to increased intestinal calcium absorption driven by 1,25-OH-vitamin D.[9] In sarcoidosis, 1α-hydroxylase produced by activated mononuclear cells stimulates PTH-independent conversion of 25-OH-vitamin D to the biologically more active 1,25-OH-vitamin D and its activity is further enhanced by inflammatory factors.[10] Clinically apparent pancreatic sarcoidosis is extremely rare and besides presentation with acute pancreatitis could also present with a mass in the pancreas or a diffusely firm nodular pancreas.[1] No signs of pulmonary invasion of the sarcoidosis were present in our patient. In all known cases (n = 7, to our best knowledge) of sarcoidosis with pancreatitis the lungs were also affected.[2-7]

Figure 1. *(A) CT abdomen depicting signs of acute pancreatitis with oedematous pancreatic tissue with indistinct margins, diffuse fat infiltration and intra-abdominal fluid collections. (B) CT abdomen showing an inhomogeneous spleen (C). Ultrasound with liver enlargement and a strongly inhomogeneous pattern*

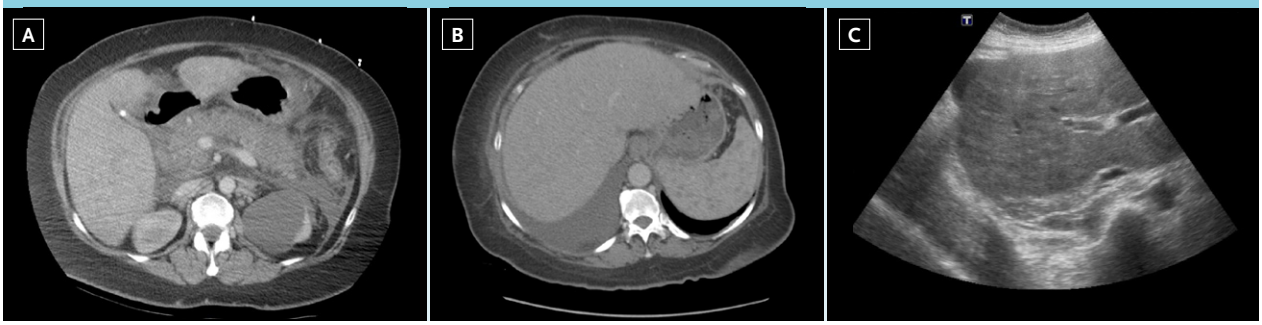
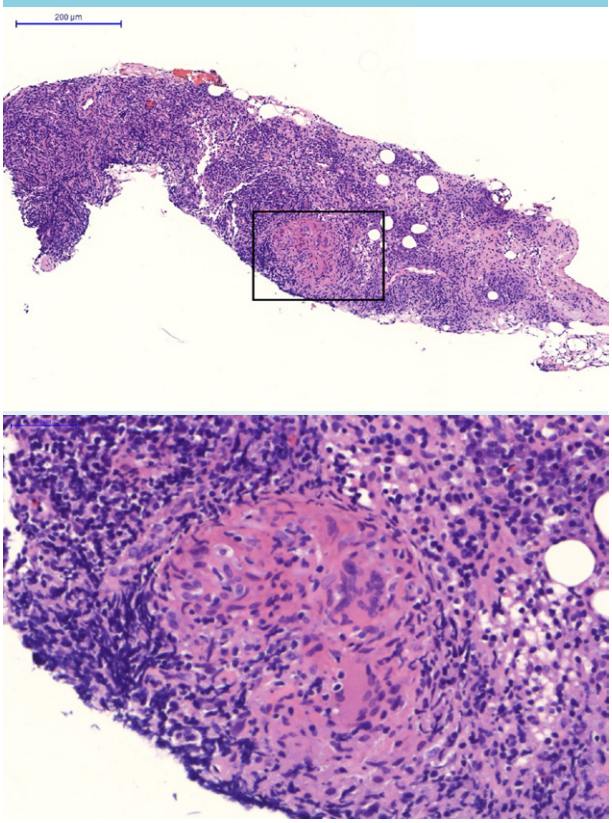


Figure 2. *Histology of omental/mesenteric lymph node with haematoxylin and eosin stain depicting non-necrotising multiple granulomas with epithelioid macrophages and multinucleated cells*



Serum ACE levels were normal in our patient and sIL-2R was strongly elevated. With treatment of the sarcoidosis, the sIL-2R levels strongly decreased. sIL-2R is more sensitive for sarcoidosis compared with ACE (sensitivity in literature: 79-98% vs. 22-73%), especially for non-pulmonary sarcoidosis, and can be used in the diagnostic work-up.[11-13] However, both parameters lack specificity.[11-13] Therefore, for the diagnosis of sarcoidosis, histopathological detection of noncaseating granulomatous is essential. Radiographic evaluation can aid to determine an accessible biopsy site. Additionally, sIL-2R has potential as a marker for disease activity, especially for non-pulmonary manifestations.[12,13]

In conclusion, acute pancreatitis can be a presenting symptom of sarcoidosis, although it appears to be extremely rare. Therefore, sarcoidosis should be considered a cause of acute pancreatitis, even in the absence of more common organic involvement such as pulmonary sarcoidosis, and especially when there is evidence of hypercalcemia.

DISCLOSURES

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REFERENCES

1. Ebert EC, Kierson M, Hagspiel KD. Gastrointestinal and hepatic manifestations of sarcoidosis. Am J Gastroenterol. 2008;103:3184.
2. Sánchez-Lozada R, Soriano-Rosas J, Gutiérrez-Vega R. Acute pancreatitis, diabetes, and sacoidosis. Case report and review of the literature. Gac Med Mex. 2004;140:343-5.
3. McCormick PA, Malone D, FitzGerald MX, FitzGerald O. Pancreatitis in sarcoidosis. Br Med J (Clin Res Ed). 1985;290:1472-73.
4. Cronin CC, Dinneen SF, Mitchell TH, Shanahan FL. Sarcoidosis, the pancreas, and diabetes mellitus. Am J Gastroenterol. 1995;90:2068.
5. Friedman HZ, Weinstein RA. Sarcoidosis of the pancreas. Arch Intern Med. 1983;143:2182-3.
6. Gupta D, Agarwal R, Singh A, Joshi K. A "respiratory" cause of abdominal pain. Eur Respir J. 2006;27:430-3.
7. Gaur S. Sarcoidosis manifested as hypercalcemic pancreatitis. South Med J. 2001;94:939-40.
8. Mithöfer K, Fernández-del Castillo C, Frick TW, Lewandrowski KB, Rattner DW, Warshaw AL. Acute hypercalcemia causes acute pancreatitis and ectopic trypsinogen activation in the rat. Gastroenterology. 1995;109:239.
9. Sharma OP. Vitamin D, calcium, and sarcoidosis. Chest. 1996;109:535.
10. Insogna KL, Dreyer BE, Mitnick M, Ellison AF, Broadus AE. Enhanced production rate of 1,25-dihydroxyvitamin D in sarcoidosis. J Clin Endocrinol Metab. 1988;66:72.
11. Ungprasert P, Carmona EM, Crowson CS, Matteson EL. Diagnostic utility of angiotensin-converting enzyme in sarcoidosis: a population-based study. Lung. 2016;194:91-5.
12. Grutters JC, Fellrath JM, Mulder L, Janssen R, van den Bosch JM, van Velzen-Blad H. Serum soluble interleukin-2 receptor measurement in patients with sarcoidosis: a clinical evaluation. Chest. 2003;124:186-95.
13. Gundlach E, Hoffmann MM, Prasse A, Heinzelman S, Ness T. Interleukin-2 receptor and angiotensin converting enzyme as markers for ocular sarcoidosis. PLoS One. 2016;11:e0147258.

CASE REPORT

An unusual causative pathogen of sepsis after a cat bite: *Anaerobiospirillum succiniciproducens*

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ABSTRACT

A 40-year-old woman with a history of liver cirrhosis presented with septic shock caused by an *Anaerobiospirillum succiniciproducens* bacteraemia after a cat bite. *A. succiniciproducens* sepsis can develop after a cat or dog bite, especially in immunocompromised hosts, or might occur after translocation from the gut flora. It is a potentially lethal infection.

INTRODUCTION

Cat bites are common and Dutch guidelines advise to prescribe antibiotic prophylaxis of amoxicillin/clavulanate for five days.[1] Infected bite wounds often contain a combination of pathogens. Common aerobic bacteria include *Pasteurella* (75%), *Streptococcus* (46%), *Staphylococcus* (35%), *Neisseria* (35%) *Moraxella* (35%) and *Corynebacterium* (28%) species. Anaerobic microorganisms are less common and include *Fusobacterium* (33%), *Porphyromonas* (30%) and *Bacteroides* (28%) species.[2] *Anaerobiospirillum succiniciproducens* is a rare Gram-negative spiral-shaped anaerobic rod that can cause life-threatening infection. With the introduction of matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS), we expect that this bacterium will be identified more often. Therefore, it is important to learn more about the characteristics, the clinical course and treatment of disease caused by this microorganism. In addition, *A. succiniciproducens* can be mistaken for *Campylobacter* species, which requires a different treatment.

In this case report, we aim to demonstrate the clinical signs of *A. succiniciproducens* sepsis and hypothesise about the source of this bacterium. In addition, we emphasise the need to consider a wide range of pathogens after a cat bite.

What was known on this topic?
Anaerobiospirillum succiniciproducens bacteraemia is a rare but serious condition. The main reservoir of this bacterium is the gastrointestinal tract of cats and dogs.

What does this add?
With the introduction of MALDI-TOF MS, *Anaerobiospirillum succiniciproducens* will probably be identified more often. Infection might occur after cat and dog bites or by translocation from the gut flora. The Dutch guideline on amoxicillin/clavulanate prophylaxis after a cat bite is adequate for this pathogen.

CASE REPORT

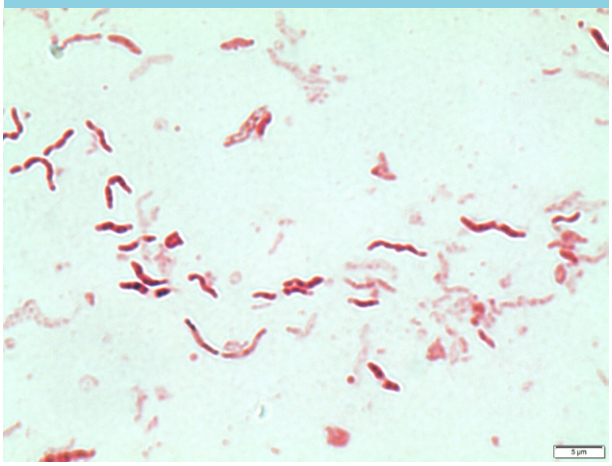
A 40-year-old woman was referred to the emergency room because of anaemia and fever. Her medical history included diabetes mellitus type 2 and liver cirrhosis (Child Pugh class C) with portal hypertension, ascites and a recent episode of bleeding oesophageal varices. Underlying alcohol abuse was suspected. Four weeks earlier she was bitten by a cat in her right thenar. She had received tetanus vaccination and a prescription for amoxicillin/clavulanate. She reported malaise and diarrhoea for one week. Five days before presentation she fell from the stairs. The body temperature was 38.1 °C, blood pressure 100/60 mmHg and heart rate 105/minute. An extensive haematoma with swelling was seen from her right hip to knee. *Table 1* shows the laboratory results. Fluid resuscitation, transfusions with erythrocyte concentrate and plasma and empiric cefuroxime and gentamicin were initiated immediately. A chest X-ray showed no infiltration.

Table 1. *Laboratory results*

Measurement	Result	Unit	Reference
Haemoglobin	2.5	mmol/l	7.5-10.0
Haematocrit	0.13	l/l	0.25-0.45
Erythrocytes	1.44	x 10^{12}/l	4.00-5.00
MCH	2193	Amol	1700-2100
MCV	111	fl	80-98
Thrombocytes	92	x 10^{9}/l	150-450
Leukocytes	15.0	x 10^{9}/l	4.0-11.0
Neutrophils	11	x 10^{9}/l	1.5-8.0
PT	24.0	Sec	12.0-15.0
aPTT	45	Sec	24-34
CRP	90.0	mg/l	< 5
Creatinine	226	µmol/l	50-95
MDRD	21	ml/ min/1.7	> 60
Sodium	129	mmol/l	137-144
Potassium	4.1	mmol/l	3.5-5.0
Bilirubin (total)	137	µmol/l	< 17
Bilirubin (direct)	71	µmol/l	< 5
Alkaline phosphatase	71	U/l	< 100
Gamma GT	98	U/l	< 40
ASAT	180	U/l	< 30
ALAT	28	U/l	< 35
LDH	578	U/l	< 250
CK	3895	U/l	< 145
Albumin	25	g/l	35-50
Haptoglobin	0.7	g/l	0.3-2.0
Vitamin B12	562	pmol/l	140-640
Folic acid	13.0	nmol/l	> 10.0
Urinalysis	normal		Normal

Computed tomography (CT) scan of thorax, abdomen and legs, primarily performed to explore other foci of bleeding and foci of infection in lungs, abdomen and the haematoma, confirmed an extensive haematoma in the right leg but no localised infection. Ultrasound excluded deep venous thrombosis. She was admitted to the intensive care unit for additional support with inotropic medication. Two days later, an anaerobic blood culture became positive. Gram staining showed Gram-negative spiral-shaped rods, suspected of *Campylobacter* species. Anaerobic subculture on sheep blood agar showed flat translucent colonies,

Figure 1. *Gram stain of the A. succiniciproducens colony*



identified as *A. succiniciproducens* by MALDI-TOF MS (Bruker Daltonics, Bremen, Germany) with a score of 2.47. *Figure 1* shows a Gram stain of the colony. Three other blood cultures, including two aerobic, became positive later with the same microorganism. The isolate appeared susceptible to penicillin (minimum inhibitory concentration (MIC) 0.25 mg/l), amoxicillin/clavulanate (MIC 0.064 mg/l) and metronidazole (MIC 4 mg/l) and resistant to clindamycin (MIC 24 mg/i).

Treatment was switched to benzylpenicillin monotherapy, and later to oral amoxicillin/ clavulanate for a total duration of 14 days. The clinical response was good. Amoxicillin/clavulanate was chosen because a purulent discharge appeared on a wound overlying the haematoma. The hypothesis of an abscess was later rejected and the haematoma reabsorbed spontaneously. After discharge the patient admitted that she had not taken the amoxicillin/ clavulanate prophylaxis after the cat bite.

DISCUSSION

A. succiniciproducens blood stream infection is a serious but rare condition. This Gram-negative, spiral, anaerobic rod was first isolated by Davis et al. from the throats and faeces of beagle dogs.[3] Two types of *Anaerobiospirillum* species have been identified: *A. succiniciproducens* and *A. thomasii*.[4] *A. succiniciproducens* mainly resides in the gastrointestinal tract of healthy dogs and cats, while *A. thomasii* was also isolated from human faeces.[3,4] Because of its morphology, *Anaerobiospirillum* can be mistaken for *Campylobacter* species, which requires another choice of antibiotic.[5]

In 33 reported patients with *A. succiniciproducens* blood stream infection, 90% had an underlying disease, 39% had a history of alcohol abuse and 11% had pre-existing liver disease.[6] Of 24 symptomatic patients, 17 (71%) had gastrointestinal symptoms and 18% had a polymicrobial blood stream infection. Mortality was

substantial at 31%. Exposure to animals (not even specified to bites) was documented in only three cases. Transmission of *A. succiniciproducens* might occur through cat bites but also through dog bites.[3]

The identification of *A. succiniciproducens* has become much easier, faster and more reliable since the introduction of MALDI-TOF MS. This technique is based on identification of the protein particles that are produced when bacteria are exposed to laser ionisation. Recognition of these products depends on the database behind the system. The Bruker database to date contains spectra of three *A. succiniciproducens* isolates. The species is also correctly identified by the Vitek MS system (bioMérieux Inc., Durham, NC).[7,8]

Correct determination of *A. succiniciproducens* is essential for choosing effective antibiotic therapy. When mistaken for *Campylobacter* species, macrolides will probably be prescribed, to which *Anaerobiospirillum* is usually resistant. It is generally susceptible to amoxicillin/clavulanate, second and third generation cephalosporins, carbapenems and fluoroquinolones.[5,7,8] As polymicrobial infection is often present, antibiotic treatment should be carefully chosen on an individual basis.

Our patient visited the emergency room four weeks before she was admitted with *A. succiniciproducens* sepsis, with an ongoing bleeding wound after a cat bite. She was treated with compresses but did not take the prescribed antibiotics. The cat bite is still a possible cause of the infection, although the incubation time seems to be rather long. A median duration of 12 hours between cat bites and the appearance of the first symptoms of infection has been described.[2] Another possibility is that *A. succiniciproducens* became part of the gastrointestinal flora in our patient, because of her daily contact with her cat and dog, and that translocation from the gut occurred, facilitated by her liver cirrhosis and portal hypertension. *A. succiniciproducens* is usually not isolated from faeces of healthy humans, but it was isolated in two patients with diarrhoea.[9,10] A third, less likely option, is that the haematoma became infected with *A. succiniciproducens*.

A. succiniciproducens is a rare but potentially lethal pathogen and infection with this microorganism should be managed with antibiotics in an early phase. Especially in immunocompromised patients or patients with underlying diseases, a complete history with attention to contact with animals is needed.

REFERENCES

1. Wichers IM, Bouma M. NHG-Behandelrichtlijn Traumatische wonden en bijtwonden. https://www.nhg.org/sites/default/files/content/nhg_org/uploads/nhg-behandelrichtlijn_ traumatische_wonden_en_bijtwonden.pdf. Accessed on 27th August 2017.
2. Abrahamian FM, Goldstein EJC. Microbiology of Animal Bite Wound Infections. Clin Microbiol Rev. 2011;24:231-46.
3. Davis CP, Cleven D, Brown J, Balish E. *Anaerobiospirillum*, a new genus of spiral-shaped bacteria. Int J Syst Bacteriol. 1976;26:498-504.
4. Malnick H. *Anaerobiospirillum thomasii* sp. nov., an anaerobic spiral bacterium isolated from the feces of cats and dogs and from diarrheal feces of humans, and emendation of the genus *Anaerobiospirillum*. Int J Syst Bacteriol. 1997;47:381-4.
5. Decroix V, Pluquet E, Choquet M, Ammenouche N, Castelain S, Guiheneuf R. Place of diagnostic tools in the identification of *Anaerobiospirillum succiniciproducens* bacteraemia. Anaerobe. 2016;39:28-30.
6. Kelesidis T. Bloodstream Infection with *Anaerobiospirillum succiniciproducens*: A Potentially Lethal Infection: South Med J. 2011;104:205-14.
7. Epstein DJ, Ernst K, Rogers R, Carmody E, Aguero-Rosenfeld M. The Brief Case: *Anaerobiospirillum succiniciproducens* Bacteremia and Pyomyositis. J Clin Microbiol. 2017;55:665-9.
8. Epstein DJ, Ernst K, Rogers R, Carmody E, Aguero-Rosenfeld M. Closing the Brief Case: *Anaerobiospirillum succiniciproducens* Bacteremia and Pyomyositis. J Clin Microbiol. 2017;55:986-7.
9. Malnick H, Williams K, Phil-Ebosie J, Levy AS. Description of a medium for isolating *Anaerobiospirillum* spp., a possible cause of zoonotic disease, from diarrheal feces and blood of humans and use of the medium in a survey of human, canine, and feline feces. J Clin Microbiol. 1990;28:1380-4.
10. Malnick H, Thomas ME, Lotay H, Robbins M. *Anaerobiospirillum* species isolated from humans with diarrhoea. J Clin Pathol. 1983;36:1097-101.

PHOTO QUIZ

A special twist in the suspicion of cancer

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CASE REPORT

A 63-year-old Dutch man presented to our hospital complaining of bloody diarrhoea, dysphagia, and bloating. He had an unintentional 5 kg weight loss during the previous week, and abdominal pain in the right upper quadrant. He was fatigued, but not feverish. He had no relevant medical history. He had no work or hobbies, and there was no history of travel to a tropical area.

Physical examination showed a grey, cachectic man, and digital rectal examination revealed blood on the examiner's glove. Laboratory results showed: CRP 81 mg/l, haemoglobin 5.5 mmol/l, MCV 82 fl, leukocytes 11.0 x 10^9/l, and albumin 19 g/l. He had normal liver and kidney function. Total IgA and anti-TTG IgA were within normal limits. Faeces culture was negative for pathogenic organisms.

A colonoscopy, gastroscopy, and an abdominal CT were then performed. No abnormalities were seen on colonoscopy. Gastroscopy showed a remarkable erosive feature of the duodenum (*figure 1*), which was biopsied (*figure 2*). Abdominal CT showed retroperitoneal and particularly mesenteric lymphadenopathy, and thickened intestinal walls in the proximal jejunum.

Figure 1. *Aspect of the duodenum on gastroscopy*

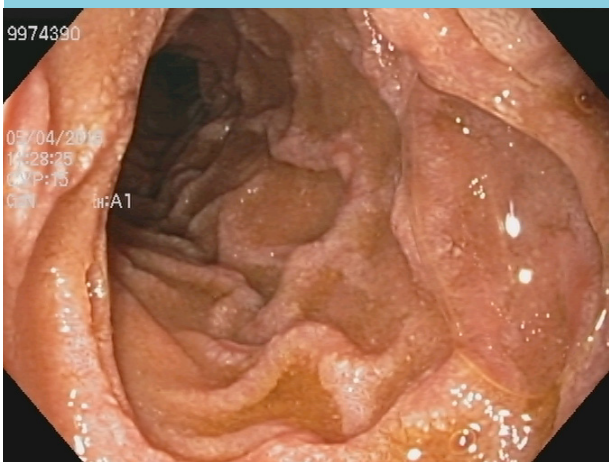
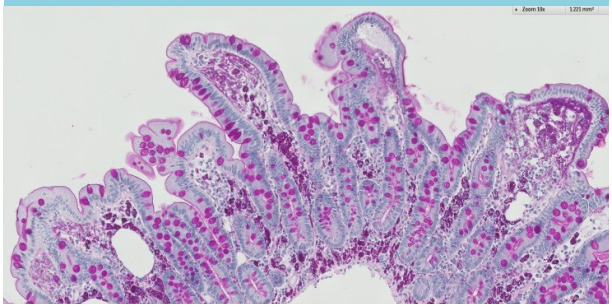


Figure 2. *Periodic acid-Schiff staining*



WHAT IS YOUR DIAGNOSIS?

See page 91 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 90)

A SPECIAL TWIST IN THE SUSPICION OF CANCER

DIAGNOSIS

The duodenal biopsies showed active inflammation with many periodic acid-Schiff (PAS)-positive macrophages in the lamina propria, strongly suggestive of Whipple's disease.

Whipple's disease is a rare, systemic infectious disease caused by *Tropheryma whipplei*.[1] The source and transmission route of this bacterium,[2] and the exact pathophysiological mechanisms involved, remain unclear, but there is sufficient evidence that indicates that patients with predisposing immunogenetic host factors (HLA-DRB1*13 and/or DQB1*06) are responsible for diminished Th1 and Th17 reactivity, which contributes to transition from the initial infection to classic Whipple's disease. This is probably why these patients show no immune response.[3] The most common symptoms are arthralgia, diarrhoea, steatorrhoea, weight loss, lymphadenopathy, abdominal pain, hypoalbuminaemia, and anaemia. In 80-90% of the cases, the first signs are seronegative arthritis and/or arthralgia, years before the gastrointestinal symptoms develop. In the late phase every organ system can be involved.[4]

Diagnosis is typically made via tissue biopsy stained with PAS, where PAS-positive macrophages in the lamina propria are observed, along with atrophy of the intestinal villi.[4]

In the work-up of our patient, inflammatory bowel disease and malignancy were high in our differential diagnosis. When we did not have a clear diagnosis after abdomen CT, gastroscopy, and colonoscopy, we performed a double-balloon endoscopy. In hindsight, this last examination was unnecessary. Although he had a typical presentation of Whipple disease, due to the rarity of this disease, we failed to consider it.

Without adequate treatment, Whipple's disease can be fatal, while antibiotic treatment can usually lead to rapid improvement. Several combinations of antibiotics have been used, the latest proposed strategy to treat *T. whipplei* infections is doxycycline 200 mg/day and hydroxychloroquine 600 mg/day for 12 months, followed by lifetime doxycycline monotherapy.[4]

We treated the patient with ceftriaxone 2.0 g/day IV for two weeks followed by cotrimoxazole 160/800 mg twice daily for one year. Regarding our patient, his signs and symptoms resolved, the laboratory results improved to within normal limits, and he began gaining weight. Because relapses are reported frequently, our patient will be monitored for life.

REFERENCES

1. Schoedon G, Goldenberger D, Forrer R, et al. Deactivation of macrophages with interleukin-4 is the key to the isolation of *Tropheryma whipplei*. J Infect Dis. 1997;176:672.
2. Fenollar F, Trani M, Davoust B, et al. Prevalence of asymptomatic *Tropheryma whipplei* carriage among humans and nonhuman primates. J Infect Dis. 2008;197:880.
3. Martinetti M, Biagi F, Badulli C, et al. The HLA Alleles DRB1*13 and DQB1*06 are associated to Whipple's disease. Gastroenterology. 2009;136:2289-94.
4. Dolmans R, Boel E, Lacle M, et al. Clinical manifestations, treatment, and diagnosis of tropheryma whipplei infections. Clin Microbiol Rev. 2017;30:529-55.

PHOTO QUIZ

An unusual cause of chronic abdominal symptoms

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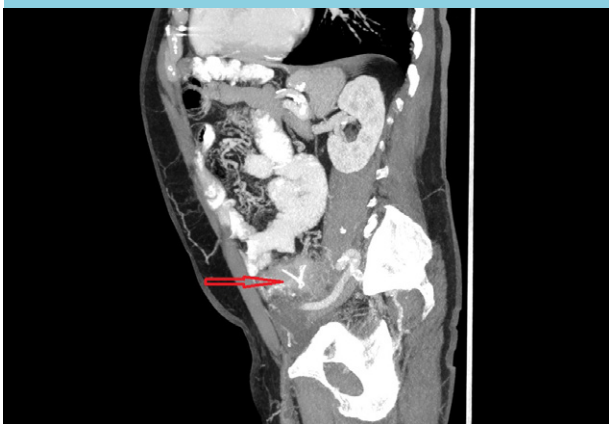
CASE REPORT

A 78-year-old man presented with a two-month history of abdominal pain, predominantly postprandial, which increased when walking, an altered defecation pattern of loose, black stools, and unintentional weight loss. The patient's past medical history was significant for gastric carcinoma, for which total gastrectomy with roux-and-y anastomosis had been performed, and for previously reported recurrent abdominal pain, for which an abdominal CT showed only diverticulosis.
All vital signs were normal. Abdominal examination revealed normal peristaltic sounds, tenderness, guarding and rigidity in the left iliac fossa, and a possible palpable infiltrate. All laboratory results were within normal limits. An abdominal CT scan was repeated.

Figure 1. *CT scan (MIP, sagittal view)*



WHAT IS YOUR DIAGNOSIS?

See page 93 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 92)

AN UNUSUAL CAUSE OF CHRONIC ABDOMINAL SYMPTOMS

DIAGNOSIS

Abdominal CT showed extensive diverticulosis and a linear foreign body lodged in the wall of the sigmoid colon, with wall thickening and local infiltration. The foreign body, a chicken bone, was removed by endoscopy. The patient made a full recovery.

Foreign body ingestion (FBI) is common,[1] and 80% of ingested foreign bodies pass through the gastrointestinal tract without complications.[2] However, these can cause obstruction, perforation or haemorrhage, or fistula formation. Perforation is experienced by only 1% of patients.[3] This is usually the result of a sharp object, such as a chicken or fish bone. Perforation usually occurs at the ileocecal junction or in the sigmoid colon.[2]

Most patients do not provide a history of FBI. It is more common in children, the elderly, alcoholics and the mentally handicapped.[1] Risk factors for FBI include the presence of dentures or sensory defects. Previous gastrointestinal surgery and diverticulosis are the most important risk factors for complications following ingestion.[2]

Patients presenting with an acute abdomen may undergo emergency surgery, usually due to a high suspicion of, for instance, appendicitis. As our patient presented with a two-month history of abdominal pain, an altered defecation pattern and weight loss, FBI was not immediately suspected. We reviewed the earlier performed abdominal CT; in retrospect, the foreign body was present. We therefore posited that the chicken bone had been lodged in the intestinal wall for a longer period.[3]

Plain radiographs can suggest a foreign body; however, CT scans are more informative.[4] Once the foreign body has passed through the stomach, asymptomatic patients can safely be observed, as 80% of foreign bodies will then pass without further complications.[2]

When peritonitis following perforation is caused by a foreign body, an exploratory laparotomy may be performed. Our patient was not diagnosed with peritonitis, nor with perforation by a foreign body. He did not present with an acute abdomen, but rather with chronic, recurrent abdominal pain, a change in defecation pattern, and weight loss.

REFERENCES

1. Kibrell FT Jr, Tepas JJ 3d, Mullen JT. Chicken bone perforation of the sigmoid colon: A report of three cases. Am Surg. 1975;41:814-7.
2. Cleator IG, Christie J. An unusual case of swallowed dental plate and perforation of the sigmoid colon. Br J Surg. 1973;60:163-5.
3. Goh BK, Chow PK, Wuah HM, Ong HS, Eu KW, Ooi LL, Wong WK: perforation of the gastrointestinal tract secondary to ingestion of foreign bodies. World J Surg. 2006,30:372-7.
4. Webb WA. Management of foreign bodies of the upper gastrointestinal tract: update. Gastrointest Endosc. 1995;41:39-51.

PHOTO QUIZ

Occupational lung disease on a farm

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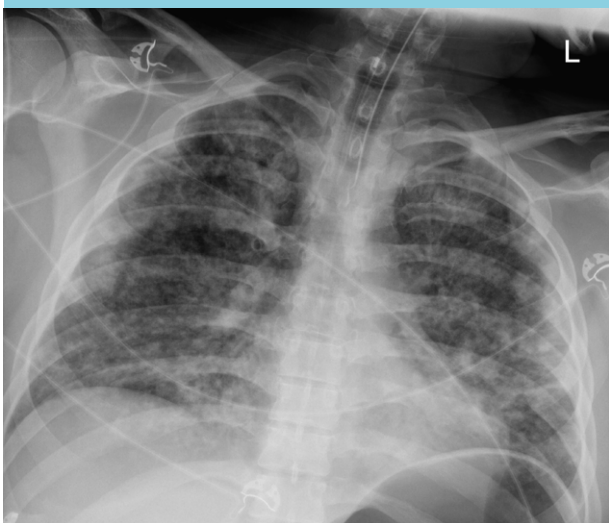
CASE REPORT

A 30-year-old male farmer with no tobacco or drug use and no significant past medical history was transferred from a local hospital to the intensive care unit of a university hospital due to hypoxia and worsening dyspnoea over the course of two days after working in a corn storage unit. Upon arrival at the local emergency department, a non-rebreather mask was required to raise the patient's oxygen saturation. Chest X-ray demonstrated bilateral ill-defined small opacities (*figure 1*). Computed tomography scan of the thorax showed diffuse ground glass central-lobular nodules (*figure 2*). The complete blood count revealed a white cell count of 23,100/mm^3 with 95% neutrophils and 2% lymphocytes. Overnight, the patient's respiratory condition deteriorated and warranted mechanical ventilation with high-dose steroids.

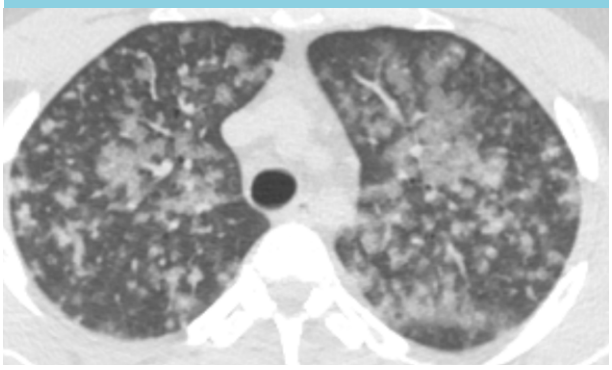
Figure 1. *Chest x-ray with bilateral ill-defined small opacities*



WHAT IS YOUR DIAGNOSIS?

See page 95 for the answer to this photo quiz.

Figure 2. *Axial computed tomography showing diffuse ground glass central-lobular nodules*



ANSWER TO PHOTO QUIZ (PAGE 94)

OCCUPATIONAL LUNG DISEASE ON A FARM

DIAGNOSIS

Silo-filler's disease presenting as ground glass central-lobular nodules on CT

Silo-filler's disease, an occupational lung disease, is a rare diagnosis in which inhalation of nitrogen dioxide, a red-brown gas, from silage fermentation causes pneumonitis and diffuse pulmonary damage.[1] Indeed, the patient's symptoms began when he was working in a corn silo the previous morning. Shortly after the exposure to an orange cloud of vapour in the corn silo, the patient experienced a burning sensation followed by progressive dyspnoea, cough, and inspiratory chest pain.

Often unrecognised, silo-filler's disease can be confused with farmer's lung, which is a hypersensitivity pneumonitis caused by exposure to mould spores or other agricultural products.[2] Patients with acute hypersensitivity pneumonitis commonly present with similar respiratory symptoms such as cough, chest tightness, and dyspnoea. Similar to silo-filler's disease, radiographic findings are characterised by a variable combination of nodular opacities and widespread ground glass opacities.[3] However, an important distinction is that hypersensitivity pneumonitis is mediated by an immunological response, in which T-cell hyperactivity underlies T-lymphocytic alveolitis.[3] Thus, bronchoalveolar lavage (BAL) with increased lymphocyte counts in the fluid would suggest a hypersensitivity reaction as opposed to silo-filler's disease where lymphocyte counts should be normal. In this patient, a BAL was not performed but both the exposure to orange vapours in a corn silo and the absence of an elevated lymphocyte count suggest the diagnosis to be silo-filler's disease, although a BAL would be necessary to definitely rule out hypersensitivity pneumonitis.

The patient's respiratory symptoms were successfully controlled by tapering of intravenous steroids to oral prednisone. Serial chest radiographs demonstrated radiographic improvement paralleling the patient's clinical improvement. The patient was discharged home with tapering of the oral prednisone and a follow-up by the pulmonary team.

Although a rare diagnosis, silo-filler's disease highlights one of the many hazards agricultural workers are susceptible to and physicians should be aware of. Workers should be encouraged to adhere to operating standards for silo use. This case also emphasises the importance of capturing an accurate and complete occupational history as the description of red-brown colour and chlorine-like odour of nitrous dioxide is vital in leading the physician to the prompt diagnosis of silo-filler's disease. Ultimately, the acute onset and life-threatening symptoms of silo-filler's disease demand increased efforts to alleviate rural health disparities through increasing health literacy in vulnerable populations susceptible to these occupational diseases.

REFERENCES

1. Grayson RR. Silage gas poisoning: nitrogen dioxide pneumonia, a new disease in agricultural workers. Ann Intern Med. 1956;45:393.
2. Gurney JW, Unger JM, Dorby CA, et al. Agricultural disorders of the lung. RadioGraphics. 1991;11:625-34.
3. Spagnolo P, Rossi G, Cavazza A, et al. Hypersensitivity pneumonitis: a comprehensive review. J Investig Allergol Clin Immunol. 2015;25:237-50.

PHOTO QUIZ

Traumatic tracheal intubation: An uncommon cause of acute airway obstruction

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CASE REPORT

A 75-year-old woman was referred to our intensive care unit (ICU) with acute upper airway obstruction. Three months prior to admission, she was admitted to a foreign hospital following neurotrauma with a subdural haematoma, for which craniotomy was performed. She underwent tracheal intubation and prolonged mechanical ventilation for three weeks, and was transferred to our hospital four weeks later. After two months of revalidation, she was admitted to our ICU with subacute signs of airway obstruction, including dyspnoea on exertion and inspiratory stridor. Clinical symptoms temporarily improved with aerosol therapy and non-invasive ventilation. Initial evaluation for the diagnosis of upper airway obstruction included a thoracic CT scan (*figure 1*). On day 5, before further evaluations could be conducted, acute upper airway obstruction recurred. Endotracheal intubation and emergency tracheostomy were unsuccessful because the tube could not be advanced beyond the stenosis; hypoxia developed, which necessitated cardiopulmonary resuscitation. Our patient failed to stabilise because of continuous respiratory deterioration, and therapy was terminated. Autopsy was performed (*figure 2*).

WHAT IS YOUR DIAGNOSIS?

See page 97 for the answer to this photo quiz.

Figure 1. *Contrast-enhanced CT image of the upper thoracic aperture and neck. (A) Coronal and (B) sagittal reconstruction showing tracheal stenosis*

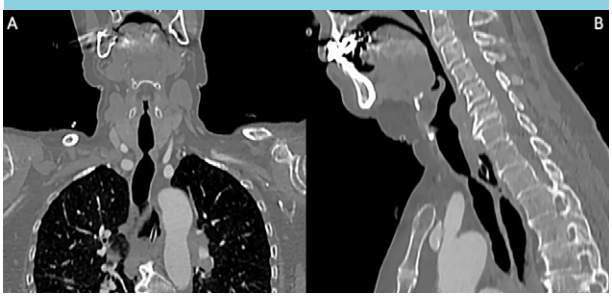
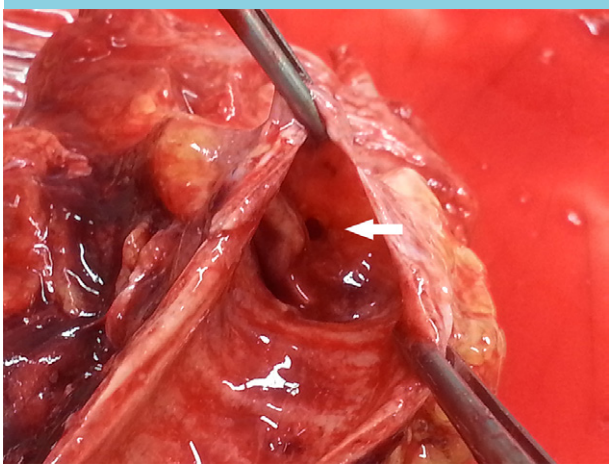


Figure 2. *Autopsy revealed concentric web-like tracheal stenosis extending into the right main bronchus, leaving only a pinpoint tracheal lumen (white arrow)*



ANSWER TO PHOTO QUIZ (PAGE 96)

TRAUMATIC TRACHEAL INTUBATION: AN UNCOMMON CAUSE OF ACUTE AIRWAY OBSTRUCTION

DIAGNOSIS

The thoracic CT scan showed severe tracheal stenosis at the level of the first thoracic vertebra. It also revealed extensive supraclavicular and mediastinal lymphadenopathy, with pleural and pericardial effusions. Histological examination of the supraclavicular lymph nodes revealed non-caseating granulomatous inflammation, with sarcoidosis as the most likely diagnosis. Autopsy revealed concentric web-like tracheal stenosis extending into the right main bronchus, leaving only a pinpoint tracheal lumen.

Causes of tracheobronchial stenosis can be either intrinsic (infectious, non-inflammatory, malignant, and iatrogenic) or extrinsic (compression and infiltrating) disease.[1]

Following endotracheal intubation, both direct tissue damage and subsequent high cuff pressure can lead to ischaemia, ultimately causing tracheal necrosis and fibrosis.[2] Therapeutic options include balloon dilations, endoscopic stenting, and laser resection. However, restenosis is common, and surgical resection can be performed when less invasive therapies fail to improve clinical outcomes.[2]

Based on our patient's medical history, which included recent endotracheal intubation, we speculate that tracheobronchial stenosis developed because of traumatic tracheal intubation and tracheal tube over-inflation with high cuff pressures. Additionally, external compression from enlarged lymph nodes might have contributed to progressive airway obstruction. Lymphadenopathy is common in sarcoidosis, with hilar and/or paratracheal mediastinal adenopathy occurring in up to 90% of patients.[3]

Our case highlights that, in patients with sarcoidosis, symptoms of upper airway obstruction resulting from traumatic tracheal intubation and tracheal tube over-inflation can rapidly worsen. Early balloon dilation and corticosteroid therapy or surgery in such cases may prove beneficial.[1,4]

REFERENCES

1. Al-Qadi MO, Artenstein AW, Braman SS. The "forgotten zone": acquired disorders of the trachea in adults. Respir Med. 2013;107:1301-13.
2. Koshkareva Y, Gaughan JP, Soliman AM. Risk factors for adult laryngotracheal stenosis: a review of 74 cases. Ann Otol Rhinol Laryngol. 2007;116:206-10.
3. Müller NL, Kullnig P, Miller RR. The CT findings of pulmonary sarcoidosis: analysis of 25 patients. AJR Am J Roentgenol. 1989;152:1179-82.
4. Shadmehr MB, Abbasidezfouli A, Farzanegan R, et al. The Role of Systemic Steroids in Postintubation Tracheal Stenosis: A Randomized Clinical Trial. Ann Thorac Surg. 2017;103:246.